Phase 2/3 Study of Arimoclomol in Inclusion Body Myositis (IBM)

A Randomized, Double-blind, Placebo-Controlled Trial

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Version Number and Date: 9.0, 08 June 2020

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International Coordinating Co-Investigator Institution: University College of London (UCL) Institute of Neurology, London, United Kingdom

Study Drug Name: Arimoclomol

Development Phase: 2/3

Date of Protocol: 08 Jun 2020

Date of previous protocol: 24 JUL 2019

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SIGNATURE PAGE

This protocol (IBM4809 version 9.0) was subjected to critical review and has been written in accordance with current ICH-GCP guidelines. The information it contains is consistent with the current risk/benefit evaluation of the test preparation as well as the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

This protocol is approved by:

Signature/Date [redacted] 06/08/2020

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[redacted], MD
International Coordinating Co-Investigator
Professor in Clinical Neurology
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LIST OF ABBREVIATIONS

Abbreviation	Description
Ab	antibody
AB-42	amyloid beta-42
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ALT	alanine aminotransferase (SGPT)
API	active pharmaceutical ingredient
AST	aspartate aminotransferase (SGOT)
β-APP	beta amyloid precursor protein
BiP	binding immunoglobulin protein
BUN	blood urea nitrogen
CE	clinical evaluator
CGIC	Clinician Global Impression of Change
CGIS	Clinician Global Impression of Severity
CHOP	C enhancer-binding protein homologous protein
CIOMS	Council for International Organizations of Medical Sciences
[redacted]	[redacted]
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DILI	Drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDL	extensor digitorum longus
EMA	European Medicines Agency
ER	endoplasmic reticulum
FDA	Food and Drug Administration
FF	finger flexor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase

Abbreviation	Description
H&E	histopathological
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDPE	high density polyethylene
HERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HRQoL	Health Related Quality of Life
HSF-1	heat shock factor-1
HSP	heat shock protein
HSR	heat shock response
IB	investigator's brochure
IBM	inclusion body myositis
IBMFRS	IBM Functional Rating Scale
IBMPFD	inclusion body myopathy with Pagets' disease and frontotemporal dementia
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
INR	International Normalised Ratio
IRB	institutional review board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
IVIg	intravenous immunoglobulin
KUMC	University of Kansas Medical Center
LDH	lactate dehydrogenase
MAR	missing at random
MCV	mean corpuscular volume
MMT	Manual Muscle Testing
MMRM	mixed model repeated measures
MSG	Muscle Study Group
mTUG	Modified Timed Up and Go
mVCP	mutant valosin-containing protein

Abbreviation	Description
MVICT	Maximal Voluntary Isometric Contraction Testing
NASH	Non-Alcoholic Steatohepatitis
NFkB	nuclear factor kappa-B
NOAEL	no-observed-adverse-effect-level
OPD	Orphan Products Development
p62	nucleoporin protein p62
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	principal investigator
PIB	Pittsburgh Compound B
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	by mouth
POP PK	population pharmacokinetics
p-Tau	tau protein
QA	quality assurance
QC	quality control
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-Item Short Form Health Survey
sIBM	sporadic inclusion body myositis
SOD1	superoxide dismutase 1
SUSAR	suspected unexpected serious adverse reaction
SMR	standard mortality ratio
TA	tibialis anterior
TBL	Total Bilirubin
TDP-43	transactive response DNA binding protein 43
t.i.d.	three times a day
UCL	University College of London
ULN	upper limit of normal
VCP	valosin-containing protein
WBC	white blood cells
wt-VCP	wild-type human valosin-containing protein

INTERNATIONAL COORDINATING INVESTIGATORS' AUTHORIZATION

Authorization of the protocol and obligations: The undersigned confirm that the protocol and all amendments, the case report forms (CRFs) and the appendices contain the necessary information and guidelines for the conduct of this study. The study will be performed and recorded according to this protocol and its approved amendments and all legal obligations and agreements will be followed as laid out below.

We have read the Phase 2/3 Study of Arimoclomol in IBM protocol dated 08 Jun 2020 (Version 9.0), and agree to abide by all provisions set forth therein. We agree to comply with the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP), EU Clinical Trials Directive, national and local regulations and the Declaration of Helsinki.

[redacted]gy

DATE: 06/08/2020

SIGNATURE: [redacted]

DATE: 9th June 2020

[redacted], MD, Professor of Neurology
International Coordinating Co-Investigator

SITE PRINCIPAL INVESTIGATOR'S AUTHORIZATION

I have read the Phase 2/3 Study of Arimoclomol in IBM protocol dated 08 Jun 2020 (Version 9.0), and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP), national and local regulations and the Declaration of Helsinki.

The amendments contained in this version of the Clinical Trial Protocol are intended to be implemented immediately by all investigators as either an Urgent Safety Measure as defined by the EU clinical trials directive or as permitted in other regions. This may mean that the implementation of the amendment is prior to approval by competent authority or IRB/IEC.

SIGNATURE: DATE:

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Print name:

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1 PROTOCOL SYNOPSIS

Title:	Phase 2/3 Study of Arimoclomol in IBM
Protocol Number	IBM4809
Type of Study	Phase 2/3
Indication	Treatment of sporadic Inclusion Body Myositis (sIBM)
Principal Investigator	[redacted], MD
Number of Study Centers	Approximately 12
Study Duration	This study is co-funded by a 4-year FDA Orphan Products Development (OPD) grant and Orphazyme. We anticipate approximately 15 months of active screening and enrollment, and 21 months of treatment and follow-up.
Participant Duration	Each participant's duration will be approximately a total of 22 months.
Population:	It is intended to randomize approximately 150 patients with the aim of achieving 75 evaluable patients in each of the two groups (arimoclomol and placebo).
Study Design	The clinical study will be a randomized, double-blind, placebo-controlled study in 150 patients with sporadic IBM followed for a 20 month treatment period. In this study there will be two treatment groups of 75 patients each, i.e., 75 patients receiving arimoclomol 400 mg three times a day (t.i.d) and the remaining 75 patients receiving placebo. Efficacy outcomes, safety laboratory tests, and adverse events will be collected. The long-term goal is to find an effective treatment for patients with sporadic IBM. A data monitoring committee (DMC) will monitor safety and tolerability during the trial according to the DMC charter. Upon completion of this study, qualified patients may enter an open-label extension study at their last treatment visit (Month 20).
Objectives	**Primary Objective** • To evaluate the efficacy of arimoclomol at a daily dosage of 1200 mg (400 mg t.i.d) compared to placebo in the treatment of sporadic IBM at 20 months. •

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	Safety Objective • To evaluate the safety and tolerability of arimoclomol at a daily dosage of 1200 mg (400 mg t.i.d.) compared to placebo in the treatment of sporadic IBM over 20 months.
Primary and Secondary Endpoints	Primary efficacy endpoint is the change from baseline to Month 20 in the IBM Functional Rating Scale (IBMFRS) total score. Secondary efficacy endpoints will include changes from baseline to Months 12 and 20 in the following measures of strength and function: • IBMFRS total score (12 months) 6 minute walk test with 2 minute distance captured • Modified Timed Up and Go (mTUG) • Muscle Strength Testing o Manual Muscle Testing (MMT) o Isometric Contraction Testing of bilateral quadriceps strength using the MicroFET • Health Assessment Questionnaire (HAQ-DI) • Grip strength using the Jamar device • SF-36 • Falls and near falls • Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) • Clinician Global Impression of Severity (CGIS) and Clinician Global Impression of Change (CGIC)
Safety Endpoints	• Adverse events (AEs); • Hematology; • Clinical chemistry; • Vital signs; • Columbia Suicide Severity Rating Scale (C-SSRS) AEs will be recorded from the time of consent to the end of the study or patient withdrawal. Physical examination and vital signs will be recorded at screening, baseline (no repeat of physical examination), 1, 2, 4, 8, 12, 16 and 20 months after the commencement of

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	continuous dosing, and at any unscheduled visits. A short-form physical examination is also included at months 3, 5 and 6. Laboratory parameters will be recorded at screening (Visit 1), 1, 2, 3, 4, 5, 6, 8, 12, 16 and 20 months after the commencement of continuous dosing, and at any unscheduled visits. The C-SSRS will be assessed at all post-baseline in-clinic visits including unscheduled visits. Unscheduled visits that are solely for the purpose of refilling medication do not require any of the safety assessments.
Other Endpoints	Exploratory endpoints include: • Population pharmacokinetics (POP PK) and exposure response analysis. • Presence of [redacted] • [redacted] (sub-study in selected sites only; in a subset of patients)
Study Drug and dosage form	Arimoclomol 200 mg capsules and matching placebo.
Doses to be studied, Dosing route and regimen	Two capsules of investigational medicinal product (IMP), each containing 200 mg (400 mg total arimoclomol or placebo) will be administered orally t.i.d. If required, the IMP can be dispersed in 10-30 mL (i.e. 1-2 tablespoons) of liquid or in a tablespoon of soft foodstuff. Dispersed in water, the IMP can also be administered via a gastric tube (as applicable).
IMP interuption, rechallenge and permanent discontinuation	If a patient experiences an intolerable adverse event, dosing may be interrupted and supportive therapy administered as required. All dosing interruptions must be discussed with the contract research organization (CRO)'s medical monitor. An interruption of up to 4 weeks (calculated from the first day of interruption) is permitted following discussion with the CRO's medical monitor prior to resuming IMP. The interruption of the dose should be as short as possible. Re-challenge with IMP in cases of increased transaminases should only be done in accordance with section 6.5.2 of the protocol. If the patient experiences the same intolerable adverse event after re-challenge with the full dose of IMP, the dose can be reduced to half, i.e., 200 mg t.i.d., following discussion with the

Title:	Phase 2/3 Study of Arimoclomol in IBM
	CRO's medical monitor. The patient must continue this dose for the remaining part of the study. If this dose is not tolerated, the IMP must be discontinued permanently. This sequence of events can be implemented only once for intolerable AEs within a given organ/body system. If the patient experiences a different intolerable AE within a different organ/body system, this sequence of events can be repeated for that AE.
Randomization	Randomization will be stratified by center and will include blocking to facilitate approximate balance in the number of subjects assigned to each treatment group within each center.
Selection Criteria	**Inclusion criteria** Study subjects must meet all of the following criteria which must be documented in the study site source documents: 1. Meet any of the European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011 categories for IBM.[1] (see Appendix 1) 2. Demonstrate being able to arise from a chair without support from another person or device 3. Able to ambulate at least 20 ft/6 meters with or without assistive device. Once arisen from the chair, participant may use any walking device, i.e. walker/frame, cane, crutches, or braces. They cannot be supported by another person and cannot use furniture or wall for support. 4. Age at onset of weakness > 45 years 5. Body weight of $\geq$ 40 kgs 6. Able to give informed consent **Exclusion Criteria** Study subjects must not meet any of the following criteria which must be documented in the study site source documents: 1. History of any of the following excludes subject participation in the study: chronic infection particularly HIV or Hepatitis B or C; cancer other than basal cell cancer less than five years prior, or other chronic serious medical illnesses. 2. Presence of any of the following on routine blood screening: WBC < 3000; platelets < 100,000; hematocrit < 30%; BUN > 30 mg/dL; creatinine > 1.5 x upper limit of normal; symptomatic liver disease with serum albumin < 3 g/dl 3. History of most recent creatine kinase >15x the upper limit of normal without any other explanation besides IBM.

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	4. History of non-compliance with other therapies. 5. Use of testosterone except for physiologic replacement doses in case of androgen deficiency. Participants must have documented proof of the androgen deficiency. 6. Coexistence of any other disease that would likely to affect outcome measures. 7. Drug or alcohol abuse within past three months. Patient has recent history (within 6 months before Screening) of chronic alcohol or drug abuse which may compromise the patient's safety or ability to participate in study activities. Cannabis for IBM symptoms will be allowed (where legal). 8. Participation in a recent drug study in the last 30 days prior to the screening visit or use of biologic agents less than 6 months prior to the screening visit. 9. Women who are lactating or pregnant, or sexually active female subjects of child-bearing potential* intending to become pregnant or unwilling to use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. Sexually active males with female partners of child-bearing potential* unwilling to use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication unless surgically sterile (vasectomy). ** Non child-bearing potential is defined as post-menopausal (minimum of 12 months with no menses and follicle-stimulating hormone in the post-menopausal range) or sterilisation (hysterectomy, oophorectomy, or bilateral tubal ligation).* *** Highly effective methods of contraception include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomised partner.* *According to the recommendations from the Clinical Trial Facilitation Group (CTFG, 2014), sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual intercourse during the trial until 1 month after the last dose of trial medication (for female subjects of child-bearing potential)*

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	and for 3 months after the last dose of trial medication (for male subjects with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. 10. Participants taking >7.5 mg prednisolone or equivalent or participants on intravenous immunoglobulin (IVIg) or other immunosuppressants within the last 3 months. Topical, nasal, and ocular corticosteroids are allowed unless they are being widely applied or the severity of the underlying condition makes them unsuitable in the Investigator's opinion. Local steroid injections are allowed. 11. Clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the upper limit of normal [ULN] for alanine aminotransferase combined with bilirubin ≥2 times the ULN; symptomatic liver disease with serum albumin < 3 g/dL; or creatinine ≥1.5 times the ULN). Laboratory tests may be repeated once at screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist, or to rule out laboratory error.
Total Sample Size	Up to 150 patients will be randomized in the study, final target is 150 patients with the aim of achieving 75 evaluable patients in each of the two groups (Arimoclomol and Placebo).
Number of Planned Visits	Following the screening and baseline visits, Visits 3 to 7 are to occur every 30 days (± 7 days) and the remaining visits are to occur every 60 days relative to baseline (± 7 days). In-person follow-up visits at the trial site are to occur at Months 1, 2, 3, 4, 5, 6, 8, 12, 16, and 20. Phone calls will be made at Months 10, 14, 18, and 21. If a patient must stop the trial medication for any reason, every effort will be made to have the patient participate in each subsequent visit as scheduled.
Statistical Methods	**Analysis of the Primary Endpoint**

Title:	Phase 2/3 Study of Arimoclomol in IBM
	The primary analysis of the primary estimand will be based on the FAS using all observations from schedueld in-clinic visits regardless of treatment adherence and used of concomittant medication. The analysis is a Mixed Model for Repeated Measurements (MMRM). The independent effects included in the model are treatment interacting with visit, trial centre as a separate main effect and baseline IBMFRS interacting with visit. An unstructured covariance matrix for IBMFRS measurements within the same patient will be used, hereby assuming that measurements from different subjects are conditionally independent. Only the in-clinic assessments of IBMFRS will contribute data to the primary analysis, whereas the assessments of IBMFRS conducted by telephone will be included in explorative analysis only. To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary estimand. The change from baseline in IBMFRS total score will also be assessed for the secondary estimand using an MMRM analysis. The MMRM will be based on all observed IBMFRS-data from scheduled visits during the on-treatmemt period. Further details on analyses of the secondary estimand and sensitivity analyses will be provided in the SAP. **Analysis of Secondary Endpoints** The Secondary endpoints will be analysed for both the primary and secondary estimands using the same imputation and analysis set-ups as described for IBMFRS. All statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. **Adverse events (AEs)** will be summarized by treatment group, maximum severity, and perceived relationship to study medication.

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	Continuous measures of safety (vital signs, laboratory test results) will be presented using descriptive statistics and the C-SSRS will be summarized. Compliance data will be summarized by treatment group, overall and by visit.

2 KEY ROLES

Funding: FDA-OPD and Orphazyme A/S

International Coordinating Investigator: [redacted], MD

International Coordinating Investigator Institution: University of Kansas Medical Center Research Institute, Inc., 3901 Rainbow Blvd/ MSN 1039, Kansas City, KS 66160

International Coordinating Co-Investigator: [redacted], MD

International Coordinating Co-Investigator Institution: University College of London (Institute of Neurology), London, United Kingdom

KUMC Project Manager: [redacted]

Medical Monitoring: Premier Research

Sponsor and provider of Drug/Placebo and Additional Funding: Orphazyme A/S

Scientific Steering Committee: [redacted] (Chair), [redacted], [redacted], [redacted], [redacted], and an Orphazyme representative

3 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Background Information

3.1.1 Name and Description of the Investigational Product

The University of Kansas Medical Center (KUMC) and University College of London (UCL) Institute of Neurology in collaboration with Orphazyme A/S are developing arimoclomol for sporadic inclusion body myositis (sIBM).

Arimoclomol was originally developed for the treatment of Amyotrophic Lateral Sclerosis (ALS) by the small biotechnology company Biorex R&D renamed CytRx Corp. and the drug is now owned by Orphazyme. The investigational product, arimoclomol, was supplied to KUMC to conduct investigator initiated clinical trials in IBM. A Phase 2 clinical study in 24 IBM patients was conducted under the investigator IND 076773 (IND Sponsor: Dr. [redacted], KUMC).

Arimoclomol (/+/-(2R),(Z)-N-[2-hydroxy-3-(piperidin-1-yl)propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (1:1)) (BRX-345) is an analog of bimoclomol, a hydroxylamine derivative that acts as a co-inducer of “heat shock” or “molecular chaperone” gene expression. Although the precise molecular mechanism of action of arimoclomol is not known, the compound has been shown to co-induce molecular chaperone genes, meaning that it further elevates the chaperone protein levels already induced by physical or metabolic stresses in cell lines and in isolated cells/tissues (see Figure 1). It apparently accomplishes this by stabilizing the active phosphorylated trimer of the transcription factor, Heat Shock Factor-1 (HSF-1). Recent evidence suggests protein misfolding and aggregation play a key role in pathogenesis in IBM. Indeed heat shock protein-70 (HSP70) levels have been shown to be increased in IBM muscle biopsies. Arimoclomol may slow down the process of protein misfolding and aggregation in IBM by helping the muscle fiber to up-regulate inducible heat shock proteins. It may also slow progression of muscle degeneration in this progressively debilitating disease.

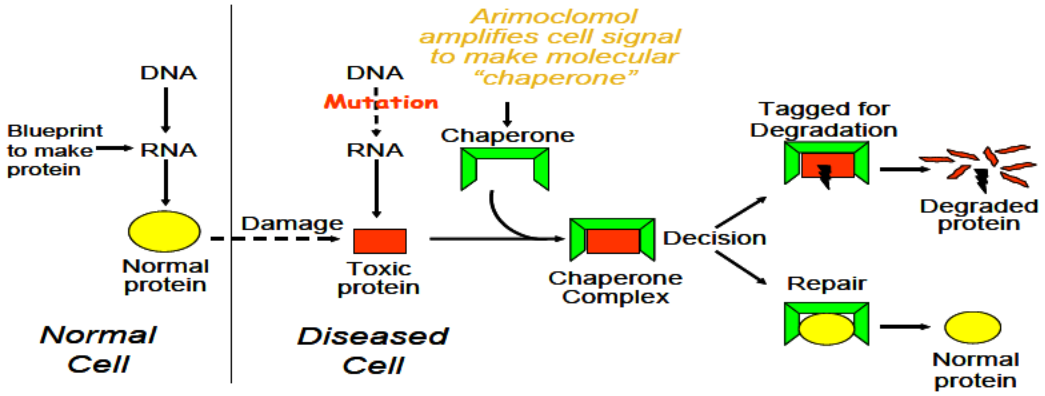

Figure 1. Arimoclomol amplifies cell signal to make molecular chaperones

3.1.2 Summary of Findings from Nonclinical In Vitro or In Vivo Studies That Have Potential Clinical Significance

3.1.2.1 In Vitro Cell Model of IBM

[redacted] is a neuroscientist at the University College of London (Institute of Neurology) who studies the effects of arimoclomol in cell cultures and in an animal model of IBM. She recently developed and characterized an in vitro model in which primary rat muscle cells in vitro were transfected with beta amyloid precursor protein (β-APP) in order to model the protein mishandling features of the disease.[2] Over-expression of human β-APP in primary rat muscle cells recapitulated several of the key pathological characteristics of IBM, including the formation of intracellular inclusion bodies which were immunoreactive for β-APP and ubiquitin as well as amyloid beta-42 (AB-42), transactive response DNA binding protein 43 (TDP-43), tau protein (p-Tau), caspase-3, HSP70 and nucleoporin protein p62 (p62). In addition, β-APP transfection resulted in activation of the nuclear factor kappa-B cells (NFkB) cascade, as demonstrated by nuclear translocation of the p65 subunit, as well as endoplasmic reticulum (ER) stress.

Using this model, [redacted] examined the effects of treatment with arimoclomol on these IBM-like pathological characteristics by assessing the following outcome measures: i) cell survival; ii) formation of inclusion bodies; iii) HSP expression; iv) TDP-43 translocation from the nucleus to the cytoplasm; v) NFkB activation; iv) ER Stress.

Following treatment with arimoclomol, there was a significant increase in cell survival, an increase in HSP70 expression and a significant reduction in the formation of ubiquitinated inclusions in β-APP transfected myotubes. In addition, in untreated β-APP transfected cultures, cytoplasmic mis-localisation of TDP-43 was observed in 52.2% of myotubes by 4 days in vitro, and this was dramatically reduced to only 2.4% of myotubes in arimoclomol-treated cultures ($P<0.0001$). Furthermore, the proportion of β-APP transfected myotubes in which the NFkB cascade was activated was also reduced by treatment with arimoclomol, so that the proportion of myotubes demonstrating NF-kB

subunit p65 nuclear staining was reduced from 43% in untreated cultures to 23% in arimoclomol-treated cultures ($p<0.05$). Finally, examination of ER calcium handling and markers of ER stress revealed that β-APP transfection resulted in a significant reduction in ER [Ca^{2+}] (an indicator of ER stress), compared to empty vector treated controls (190nM compared to 280nM; $p<0.05$), a deficit that was completely prevented by arimoclomol (ER [Ca^{2+}] 290nM). This dramatic and beneficial effect of arimoclomol on ER stress was reflected in a reduction in the expression of the ER stress markers C-enhancer-binding protein homologous protein (CHOP) and binding immunoglobulin protein (BiP) in arimoclomol-treated β-APP transfected myotubes, compared to untreated cultures.[3-5]

Together these results indicate that arimoclomol ameliorates several key pathological features of IBM-like pathology, at least in an in vitro model of the disease (see Figure 2).

Figure 2. Over-expression of β-APP and exposure to inflammatory mediators induces IBM like pathology in cultured myocytes which is ameliorated by treatment with arimoclomol

Formation of cytoplasmic inclusion bodies in myocytes immunoreactive for (a) β-APP and ubiquitin and (b) TDP-43. The bar chart (c) shows the percentage of myocytes containing ubiquitinated inclusion bodies. (d) Expression of TDP-43 (green) following β-APP transfection and arimoclomol treatment and (e) quantification of the number of cells with cytoplasmic mislocalization of TDP-43. (f) TDP-43 expression (green) following exposure to inflammatory mediators and arimoclomol treatment and (g) quantification of TDP-43 mislocalization in inflammatory mediator exposed cultures. (h) Western blot analysis of TDP-43 expression in myocyte cultures exposed to inflammatory mediators in the presence and absence of arimoclomol. (i) Images show the expression of NFkB subunit p65 (green) in β-APP transfected cultures (DAPI labelled nuclei in blue) and (j) cultures exposed to inflammatory mediators, in the presence and absence of arimoclomol. (k) The bar chart shows the percentage of cells

with nuclear NFkB subunit p65 under all culture conditions investigated. Error bars = S.E.M; Scale bars: a, b =10μm, d, i and j =20μm

3.1.2.2 In Vivo Model of IBM

Professor [redacted] has recently completed an efficacy trial of arimoclomol in a mouse model which recapitulates several key features of IBM.[6] Patients with an A232E mutation in valosin-containing protein (VCP), a protein involved in numerous cellular functions including protein degradation, present with a condition called inclusion body myopathy with Pagets' disease and frontotemporal dementia (IBMPFD). Transgenic mice over-expressing the same human mutation in VCP display a muscle pathology that closely resembles that of IBM, including muscle weakness and histopathological signs of IBM such as rimmed vacuoles and TDP-43 and ubiquitin-positive pathology. Dr. Greensmith's team treated mutant VCP (mVCP) mice treated with arimoclomol (120 mg/kg per day, orally, in drinking water) from the start of symptom onset at 4 months until 14 months of age, a late stage of disease. Transgenic mice over-expressing wild-type human VCP (wt-VCP) were used as controls, and 10 male mice per group were studied. Muscle strength was assessed longitudinally by performing grip-strength measurements fortnightly from the start of treatment (see Figure 3a). In addition, muscle force was also established using isometric muscle force measurements performed on terminally anaesthetized mice at 14 months of age (Figure 3b,c). In control wt-VCP mice, there was no significant reduction in grip strength relative to body weight between 4 (6.44g +/- 0.49 SEM) and 14 months of age (5.91g +/- 0.62 SEM). In contrast, in mVCP mice, there was a 44.1% reduction in grip strength during the same period (from 7.19 g +/- 0.39g SEM to 4.02g +/- 0.3g SEM). However, in mVCP mice treated with arimoclomol, there was no significant reduction in grip strength over time; with only a mild reduction from 6.24g +/- 0.42g SEM to 5.18g +/- 0.34g SEM by 14 months. These longitudinal readouts of muscle strength were reflected in the maximal tetanic force measurements obtained from extensor digitorum longus (EDL) muscles of mice examined at 14 months of age. In mVCP mice, EDL muscles generated significantly less force (16.59g +/- 1.86 g SEM) than EDL muscles in wt-VCP controls (24.18g +/- 1.94g SEM). However, in arimoclomol treated mVCP mice, there was no significant difference in the force output of EDL muscles (22.47g+/- 1.84g SEM) compared to controls. These results show that treatment with arimoclomol prevents the loss in muscle force that occurs as disease progresses in mVCP mice.

Histological assessment of the hindlimb muscles of mVCP mice showed remarkable pathological changes which correspond with characteristic IBM features seen in patient muscle biopsies (Figure 3d,e). Tibialis anterior (TA) muscles of mVCP mice showed clear signs of degenerating and atrophied fibers of irregular sizes, infiltration of inflammatory cells, presence of vacuoles and proteinaceous aggregates. Furthermore, an increase in the number of centralized nuclei was observed which is regarded as a feature of regenerating muscle fibers. Examination of muscle from arimoclomol treated mVCP mice however showed a greatly reduced level of degenerating and atrophied fibers (Figure 3f). Quantification of the number fibers containing centralized nuclei showed that Arimoclomol treated mVCP mice had significantly more fibers with centralized nuclei

(35.28% +/- 4.51% SEM) compared to untreated mVCP mice (18.67% +/- 3.43% SEM) or wt-VCP mice (3.09% +/- 3.39% SEM), suggesting a greater extent of regeneration in the muscle of arimoclomol treated mice.

Since arimoclomol is known to be a co-inducer of the HSR, [redacted] also examined whether the beneficial effects of arimoclomol on the muscle pathology in mVCP mice was reflected in a change in expression of HSP70. As can be seen in Figure 3h, Western blot analysis of muscle from mVCP mice treated with arimoclomol showed a two-fold increase in the expression of HSP70 compared to that of untreated mVCP mice.

The results of this *in vivo* efficacy study in a mouse that models key aspects of IBM confirm that treatment with arimoclomol prevents the decline in muscle strength and improves the histopathological characteristics of IBM, most likely as a result of an upregulation in HSPs.

Figure 3. Treatment with arimoclomol prevents the loss in muscle force and appearance of IBM-like pathology in mutant VCP mice

a) Longitudinal analysis of grip strength shows that there is a significant decline in grip strength in mVCP mice between 4 and 14 months of age which is prevented in mice treated with arimoclomol. b) Typical traces of maximum tetanic force of EDL muscles in anaesthetized mVCP and arimoclomol treated mVCP mice are shown. c) The bar chart shows that treatment with arimoclomol prevents the loss in EDL force that occurs in mVCP mice by 14 months of age. Histopathological (H&E) analysis of TA muscles reveals the presence of key IBM-like pathological characteristics in mVCP mice. Compared to wt-VCP mice (d) TA muscles from mVCP mice (ei-v) show atrophied and degenerating fibers, inflammatory cell infiltration, centralized nuclei and the presence of rimmed vacuoles. In contrast, TA muscles from mVCP mice treated with arimoclomol shows few if any of these pathological changes (f). Quantification of the number of fibers with centralized nuclei (g) shows that there is a significant increase in the number of fibers with centralized nuclei in arimoclomol-treated mVCP TA muscles which is indicative of active regeneration. h) Western blot analysis shows that here is a significant increase in the expression of HSP70 in TA muscles of mVCP mice treated with arimoclomol, compared to either untreated mVCP or wt-VCP mice.[6]

3.1.3 Summary of Human Clinical Pilot Research Data

A randomized controlled pilot study in 24 IBM subjects, 18 of whom received arimoclomol 100 mg PO TID for four months and 8 were on placebo.[6] The IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p value approaching significance at 8 months. Results from the clinical

proof-of-concept trial in IBM patients showed that arimoclomol was both safe and well tolerated, and identified a promising positive trend of effect on disease outcome measures although the study was not powered for efficacy.

3.1.4 Discussion of Important Literature and Data that are Relevant to the Trial and that Provide Background for the Trial

IBM is the most common progressive and debilitating muscle disease beginning in persons over age 50 years, with an annual incidence estimated at 2.2 to 7.9 per million.[8-16,20] Because biopsies of IBM muscle contain lymphocytic inflammatory cells, IBM was originally grouped with the inflammatory idiopathic myopathies: polymyositis and dermatomyositis. However, pathologic studies during the past 25 years have clearly defined it as a unique pathogenic entity.[17,18] IBM is a progressive, debilitating disease causing both proximal and distal muscle weakness, characteristically most prominent in the quadriceps and finger flexors.[19-21] Over time it can lead to severe disability, including falls due to quadriceps muscle weakness and foot drop, dysphagia, and eventually respiratory muscle weakness.[11,19, 22-23] Sporadic inclusion body myositis (sIBM) is the most frequently occurring form of IBM; hereditary forms of IBM occur very rarely. sIBM seldom affects patients under 40 and is much more common over the age of 50. Men are affected more frequently than women.[24] The natural history of IBM has been followed prospectively in three studies.[25,26,29] Rose et al. followed 11 subjects for six months, and found an overall four percent decrease of strength from baseline.[26] Data collection from 136 IBM patients from the Paris and Oxford groups was completed either during a clinic visit (52%), or by extraction from previous medical records (48%). After a median duration of 14 years from onset, 75% of patients had significant walking difficulties and 37% used a wheelchair.[29] Patients were treated with immunosuppression agents (prednisone, intravenous immunoglobulins, methotrexate or azathioprine) for a median duration of 41 months were more severely disabled on last assessment. In a 12-year follow-up study, 46/64 Dutch patients with sporadic IBM follow-up patients had died; with six patients (13%) having end-of-life care interventions.[60] The high frequency in sIBM is about one-third of the rate found in amyotrophic lateral sclerosis, and it highlights the heavy disease burden in the final stage. While life expectancy is not shortened, the causes of death differed from an age-matched Dutch general population in that aspiration pneumonia was significantly more frequent as a cause of death in sIBM. In another study, patients with sIBM who were aged 41 years and older had an approximately 7-fold higher risk of premature mortality than the age-matched external comparison population (standard mortality ratio [SMR], 6.58; 95% CI, 5.6–7.7). As expected, the risk of premature mortality in patients with sIBM decreased with increasing age, but was still approximately 5-fold higher than the age-matched external comparison population in patients over 70 years of age (SMR, 4.82; 95% CI, 3.9–5.9).[61] There is also preliminary evidence for increased mortality in sIBM patients who harbor [redacted][62]

We performed a retrospective chart review of 51 IBM cases from the University of Kansas.[18,30] After a 7.5-year mean disease duration, 56% of our cases required an assistive device, with 20% requiring a wheelchair or motorized scooter (Table 1).[18]

Table 1: Retrospective chart review of IBM from 2000 to 2010 at KUMC

Male: female ratio	1.7:1
Ethnicity (n=51)	49 Caucasian; 2 Hispanics
Mean age at onset (yrs)	61 (45-80)
Symptom onset before age 50 yrs:	12%
Mean time to diagnosis (yrs)	5.1 (1-15)
Mean follow up period (yrs)	2.5 (0.5-8)
CK (IU/L)	609 (59-3000)
Nerve conductions with axon loss neuropathy	32%
Electromyography	60% irritative myopathy 12% non-irritative myopathy 28% mixed neuropathic/ myopathic pattern
Asymmetry	90%
Non-dominant side weaker	85%
Typical phenotype: Weak Finger Flexor (FF) and quadriceps (quads)	39/51 (76%): 13 - Classic phenotype (FF and quads weakest) 11 - Classic FF, no preferential quads weakness 6 - Classic quads, no preferential FF weakness 9 - FF and quads weak but not weakest
Atypical phenotype	12/51 (24%): 5/12: classic FF with leg weakness sparing quads 4/12: limb-girdle weakness 3/12: other atypical phenotypes (FF arm only, hip flexion/ankle dorsiflexion, facioscapulohumeral)
Muscle pathology	43: inflammation and rimmed vacuoles 8: phenotypic IBM with inflammation but no vacuoles
Mobility Outcome	75%: recurrent falls 56%: assistive device use at mean 7.5 years 20%: wheelchair or scooter
Bulbar dysfunction	51%: dysphagia 55%: facial weakness

3.1.4.1 Pathology

There is also myonuclear degeneration early on in IBM because the majority of rimmed vacuoles are lined with nuclear membrane proteins. IBM myonuclei are often abnormally filled with neurofilaments and this may be the earliest detectable pathologic change in IBM.[10]

In IBM, myofibers contain nonnuclear sarcoplasmic TDP-43 accumulations together with a reduction of the normal nuclear TDP-43 content. This suggests that TDP-43 has redistributed from nuclei to sarcoplasm in a large percentage of IBM myofibers.[31] The extranuclear accumulation of TDP-43 may be toxic to cells perhaps through altered binding to and splicing of mRNA. There are similarly cytoplasmic aggregates of sequestosome 1/p62 (referred to from here on as p62) which is encoded for by the SQSTM1 gene. This multifunction protein participates in the autophagy pathway and transduction pathways such as nuclear factor kappaB (NFkB) signaling and apoptosis.[32] Immunohistochemically, TDP-43 and p62 were the most sensitive markers, accumulating in all definite IBM and in 31% and 37%, respectively, of possible IBM cases.[33] Therefore, IBM muscle accumulates multiple toxic protein aggregates suggesting a disorder of protein homeostasis.

The degenerative theory of IBM hypothesizes that IBM is a degenerative muscle disease occurring in an aged cellular environment, associated with cellular accumulation and aggregation of several proteins, involving abnormal signal transduction and transcription, protein misfolding, inhibition of the cellular protein degradation pathway, and mitochondrial dysfunction.[34] The lymphocytic infiltrate is considered likely to be secondary to muscle fiber degeneration.

A model of pathogenesis in IBM has been proposed (see Figure 4).[35] In this model the aging muscle intracellular environment, combined with environmental factors like oxidative stress, viruses, or other toxins, and in combination with mutations in predisposing genes leads to up-regulation of Aβ precursor protein. This leads to abnormal accumulation of Aβ 40 and 42 fragments. The Aβ 42 fragment in particular has a hydrophilic face and tends to aggregate into cytotoxic oligomers. Increased transcription of Aβ precursor protein leads to up-regulation of other proteins which co-aggregate with Aβ fragments. The effects of these toxic oligomers cause oxidative stress in the cell, phosphorylation of tau protein, an increase in misfolded proteins, and inhibition of the proteasome protein degradation pathway. This creates a positive feedback cascade. The cell increases its levels of heat shock proteins to help counteract this increase in misfolded proteins, in particular HSP70, but cannot keep up with increasing levels of toxic protein products. This upregulation of Aβ precursor protein can also lead to mitochondrial defects, further exacerbating the cycle. In support of this theory, cultured muscle fibers with overexpressing Aβ precursor proteins display similar pathology to that seen in human IBM muscle biopsies. Accumulation of these misfolded proteins eventually leads to the characteristic Aβ amyloid inclusions and paired helical fibers containing phosphorylated tau seen in IBM muscle biopsy specimens.[34,36-38]

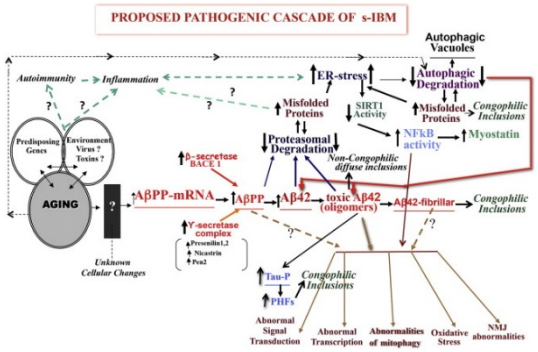

Figure 4. Proposed pathogenic cascade of sIBM[35]

3.1.4.2 Protein Misfolding

Many systemic and neurodegenerative disorders, termed 'protein-misfolding disorders' are characterized by the accumulation of intracellular or extracellular protein aggregates.[38] The initiating event in the disease process may be a crucial conformational change that occurs in the disease protein, possibly mediated by physical trauma, oxidative damage, or an infectious agent that leads to protein aggregates. These aggregates, or more likely their intermediate oligomeric precursor forms, can act to catalyze the process of additional aggregation, accelerating the "sequestration" of the normal protein and potentially trapping other important proteins that are prone to aggregation. In most instances these aggregated protein products are found to be cytotoxic, although the exact mechanism of toxicity is unclear.

A highly conserved class of proteins called molecular chaperones has evolved to prevent inappropriate interactions within and between non-native polypeptides, to enhance the efficiency of *de novo* protein folding, and to promote the refolding repair of proteins that have become misfolded as a result of cellular stress[39-42] (see Figure 5). In addition to this protein repair activity, chaperones can mediate targeting to the proteasome system or to lysosomes, resulting in selective degradation of the misfolded protein when the chaperones cannot repair the misfolded proteins. These activities of the molecular chaperones may be sufficient to prevent the normal accumulation of misfolded proteins. Under conditions of cellular stress, chaperone activity is increased, adjusting to the consequent increase in damaged proteins. However, under certain pathological conditions (perhaps due to prolonged exposure during chronic disease), the capacity of this protein quality control machinery can be exceeded, and misfolded proteins accumulate to dangerous levels.

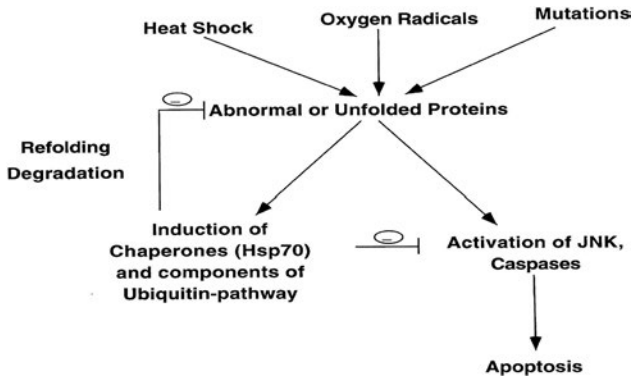

Figure 5. Schematic of the mechanism of action of HSP70[40]

3.1.4.3 Primary Endpoint: IBMFRS

The Inclusion Body Myositis Functional Rating Scale (IBMFRS) is a quickly administered (10-minute) ordinal rating scale (ratings 0-40) used to determine patients' assessment of their capability and independence in 10 functional activities. The scale was developed by the Muscle Study Group (MSG) investigators and was utilized in the beta-interferon-IBM trials.[27,28] All 10 activities are relevant in IBM. The advantages of the IBMFRS are that the categories are relevant to IBM, it is a sensitive and reliable tool for assessing activities of daily living function in patients with IBM, and it is quickly administered. In the beta-interferon trial, the IBMFRS correlated well with MVICT, MMT, SF-36, and the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS).[43]

The IBMFRS (see Appendix 2) was derived from the ALSFRS which is another patient-derived subjective scale currently accepted as the primary endpoint measure for nearly all ALS clinical trials for the last 15 years. The IBMFRS has been validated in its use with IBM patients as it correlated well with objective strength measures (Maximum Voluntary Isometric Contraction and Manual Muscle Testing) and quality of life as assessed by the SF-36.[44] Recently, we presented an analysis of prospective IBMFRS data collected over several years in 127 IBM cases from the UK and USA.[44]

The IBMFRS includes 10 measures (swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, changing position from sitting to standing, walking, and climbing stairs), each graded on a Likert scale from 0 (being unable to perform) to 4 (normal). Sum of the 10 items gives a value between 0 and 40, with a higher score representing less functional limitation.

3.1.5 Importance of the Study and Any Relevant Treatment Issues or Controversies

In the US, the true prevalence of IBM is unknown, but is conservatively estimated at 5-10 cases per million and the upper end of the prevalence estimate range is 71 per million.[8] There are no effective treatments for IBM; the patient's disease continues to progress

regardless of therapy. No pharmaceutical has been proven to be effective for IBM and therefore there is a significant unmet need for these patients.

3.1.5.1 Rationale

HSP70 is increased 4.5 times above normal in muscle biopsies of patients with IBM and has been shown by immunocytochemistry to co-localize with Aβ amyloid deposits. In the superoxide dismutase 1 (SOD1) mouse model of amyotrophic lateral sclerosis, arimoclomol significantly increased levels of HSP70 and HSP90 in the spinal cords of mice and increased survival[42] (see Figure 6). In a manner similar to ALS, HSP70 levels are already upregulated in IBM; however, they may be sequestered in Aβ amyloid aggregates and thus rendered less effective. Increasing the availability of heat shock proteins in IBM may therefore be of therapeutic importance.

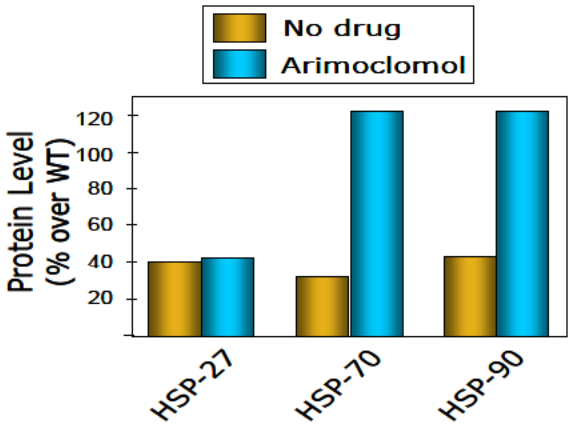

Figure 6. Arimoclomol-induced increase in HSP70 and HSP90 in SOD1 mice[42]

Arimoclomol has also been shown to interact with acidic lipids, including cardiolipin, a lipid component specific to the mitochondria. This lipid interaction may play a role in the protection of the mitochondria and prevention of apoptosis. In IBM cell culture models, mitochondria are thought to be affected by Aβ precursor protein and Aβ fragment over-expression. Mitochondrial abnormalities are found in IBM muscle biopsies at a higher frequency than in the normal population. Arimoclomol may help stabilize mitochondria in this environment.

In vitro, both β-APP overexpression and exposure to inflammatory mediators induced degenerative IBM-like pathology in myocytes, including an increase in the formation of ubiquitinated inclusion bodies. Treatment with arimoclomol significantly reduced inclusion body formation, indicating an improvement in protein handling, most likely as a result of an upregulation of the HSR, in particular an enhanced HSP70 expression. Both models also recapitulated the increase in mis-localised TDP-43 observed in IBM patient myofibres. TDP-43 is cleaved by caspase-3,[45] allowing the C-terminus to leave the nucleus, thus linking its translocation to high levels of cell stress. Arimoclomol also significantly reduced TDP-43 mislocalisation, and reduced TDP-43 levels in cultures

exposed to inflammatory mediators, suggesting lower levels of cell stress. Indeed, both β-APP over-expression and inflammatory mediators induced cell death, which was significantly reduced by arimoclomol.

Nuclear translocation of the NFkB subunit p65 was examined as an indication of NFkB activation, which was observed following exposure to IL1β and TNFα. β-APP over-expression also induced NFκB activation, in keeping with cellular models of Alzheimer's disease, in which Aβ42 has been shown to activate the inflammatory cascade.[46] Arimoclomol had an inhibitory effect on NFκB activation in both models, which is likely to reflect HSR augmentation, given the established ability of HSPs to down-regulate the NFκB cascade.[47]

Arimoclomol also significantly reduced the disruption in ER calcium homeostasis induced in both IBM models and consequently reduced the ER stress response, a key mechanism involved in handling aberrant proteins.[6] This was reflected by restoration of cytosolic calcium levels towards control levels. Indeed, in TNFα treated cultures, the reduction in cytosolic calcium was entirely prevented by arimoclomol, as was the expression of the ER stress mediator CHOP. This protective effect of arimoclomol is likely to reflect, at least in part, the chaperone activity of augmented HSP70 levels which serves to improve the efficiency of protein handling and repair or degradation of misfolded proteins.

Examination of the two major protein degradation pathways in the culture models revealed disruption in both proteasome function and increased autophagy. However, arimoclomol had no effect on proteasome function, although formation of mature autophagosomes was reduced, suggesting a reduced misfolded protein load in the lysosomal pathway.

In vivo, treatment of mVCP mice with arimoclomol between 4-14 months of age significantly improved the pathological features and functional deficits characteristic of the inclusion body myopathy.[6] Thus, in arimoclomol-treated mVCP mice an increase in muscle strength was observed and a reduction in key pathological hallmarks of IBM, including a decrease in ubiquitin expression and a reduction in cytoplasmic mis-localisation of TDP-43, accompanied by an increase in HSP expression.

Previous experimental clinical trials in IBM have only tested agents directed at the inflammatory component of pathology and all were ineffective.[10,13,48-50] Whether the degenerative aspect of IBM is primary to the pathogenesis or not, it very likely plays a role in the deleterious effects in muscle, and may be a potential therapeutic target. Protein homeostasis (proteostasis) is essential for normal cellular functions[3] and in conditions of cellular stress, proteins can become unfolded or misfolded, leading to their aberrant aggregation.[4]

Protein misfolding is normally managed by endogenous chaperone proteins[5], which prevent aberrant protein-protein interactions and promote correct protein folding. HSPs are a family of ubiquitously expressed protein chaperones, which are up-regulated following stress-induced activation of the heat shock response (HSR), an endogenous cytoprotective mechanism. Since the HSR declines with advanced age[2], up-regulation of the HSR in disorders in which there is evidence of protein mishandling, such as IBM, may be of therapeutic value.

A randomized controlled pilot study was conducted in 24 IBM subjects, 18 of whom received arimoclomol 100 mg PO TID for four months and 8 were on placebo. The IBM functional rating scale (IBMFRS) decline at 1 year was less in the arimoclomol group compared to placebo with the p value approaching significance at 8 months. Results from the clinical proof-of-concept trial in IBM patients showed that arimoclomol was both safe and well tolerated, and identified a promising positive trend of effect on disease outcome measures although the study was not powered for efficacy.

These findings provide compelling evidence of the beneficial effects of arimoclomol in *in vitro* and *in vivo* models of IBM, which support clinical assessment of its effects in IBM patients. However, up-regulation in HSP expression by arimoclomol was clearly established in both the *in vitro* and *in vivo* models, as previously reported.[42]

A Type C guidance (written responses only) was received under IND 076773 from the Food and Drug Administration (FDA) with regards to a Phase 2/3 protocol with on 21 June 2016 (Reference ID 3948721). Initially, the Sponsor proposed 0 mg (placebo), 100 mg t.i.d and 200 mg t.i.d. as the doses for the protocol. FDA recommended to select a higher dose that may be closer to the maximum tolerated dose. Therefore, clarification was sought on behalf of the Sponsor of the IND regarding the proposed doses for the protocol, where the doses of 0 mg (placebo), 200 mg t.i.d and 400 mg t.i.d. were proposed. The Agency agreed to the higher dosing of 400 mg t.i.d. and the proposal to increase the lower dose to 200 mg t.i.d. Statistical evaluation has shown that to perform a three arm study, we would need to double our sample size to demonstrate the same efficacy as with a two arm study. Given this is a rare disease with limited total patients, the current study design is a two-arm study comparing placebo versus arimoclomol 400 mg t.i.d.

This proposal for higher dosing (400 mg t.i.d.) is based on nonclinical safety data and previous human exposure; the nonclinical and clinical study reports are submitted to IND 071269; study numbers included in parenthesis are summarized below:

Nonclinical:

In vitro data

- Dose proportionality is established in relevant in human cell line over a wide range, 10-400 µM.
- No effect on human ether-a-go-go-related gene (hERG) potassium channels (ARIM-SF-001)
- No CYP Inhibition (ARIM-AD-003)
- Weak inhibitor of the OCT 2 transporter; IC50 at 10 µM (CYP0882_R1)

Toxicity data

- 19 nonclinical toxicological studies have been performed with arimoclomol in mice, rats and dogs
- Dogs: no-observed-adverse-effect-level (NOAEL) at 160 mg/kg/day (80 mg/kg BID) PO determined in 52 weeks study (ARIM-TX-004)

- Rats: NOAEL at 375 mg/kg/day PO determined in 28 day toxicology study in rats
- Lethal dose 1800 mg/kg PO QD. The test item arimoclomol administered orally to rats in doses 200, 400 and 900 mg/kg respectively over 180 days did not cause any toxic lesions detectable by histological examination (PREST-013)

Clinical:

Extensive human exposure to arimoclomol

- 7 (seven) Phase I studies were completed with dose levels ranging from 50 mg to 1800 mg
- Maximum single dose administered in human being was 800 mg
- Maximum repeated dose was 600 mg t.i.d. for 5 days (AALS-005)
- Renal safety was assessed in a 28 day Phase I study with 400mg t.i.d (1200 mg daily) or placebo t.i.d. administered for 28 days was safe and well tolerated. There were no deaths, no serious adverse events (AEs) and no other significant AEs. (AALS-010)
- Cmax observed at 1628 ng/ml (3.2 µM) (Healthy male volunteers) (AALS-010)
- Higher metabolite exposure in animals than humans

Based on the minimum safety factor of 10 for calculating the human equivalent doses, the current study highest dose of 1200 mg daily (~ 17 mg/kg based on average human body weight of 70 kg) is much lower than the calculated highest safe dose of 6300 mg daily, i.e. 70 kg x 90 mg (1/10 of safe dose tested in Pre-ST-013). The proposed dose of 400 mg t.i.d. was also well tolerated in the 28-day Phase I study in healthy human volunteers. The maximum tolerated dose for humans is not known but the highest dose used in healthy volunteers is 1800 mg/day.

Preliminary data from the pilot Phase II clinical study indicate that arimoclomol 100 mg p.o. t.i.d. is safe and well-tolerated in IBM.[6] Given the observed positive IBMFRS and MMT trends from the pilot study, further investigation of arimoclomol in a larger IBM patient population is warranted. While a dosage of 100 mg t.i.d. was used in the pilot Phase 2 study, a 400 mg t.i.d. dosage will be used in the Phase 2/3 clinical study.

3.1.6 Potential Risks and Benefits

3.1.6.1 Safety and Tolerability

A total of 10 clinical studies with arimoclomol have been conducted: 7 studies in healthy subjects, 2 studies in patients with ALS, and 1 study in sIBM.

Data from the completed studies indicate that arimoclomol may lead to a drug-related increase in serum creatinine and a decrease in mean creatinine clearance. There was no change in glomerular filtration rate (GFR) and serum cystatin C, suggesting an inhibitory effect of arimoclomol on tubular secretion of creatinine. The increase in serum creatinine may be explained by a weak interaction of arimoclomol with the OCT2 transporter. See the current version of the Investigator's Brochure for further information.

In a completed investigator initiated study in sIBM (10656), there were no significant differences between treatment groups regarding the rate, type, and severity of AEs. There were 8 possibly treatment-related AEs in the placebo group and 14 with arimoclomol, the most common being gastrointestinal.[6]

Increases in transaminases (ALT/AST) have been observed in a minority of patients treated with blinded IMP in ongoing trials with arimoclomol. The maximum increase has been above 20x upper limit of normal (ULN). The values have returned to baseline either during treatment or after discontinuation of blinded IMP.

3.1.6.2 Known Potential Benefits

Trials assessing immunotherapeutic agents have not demonstrated significant efficacy against IBM. In experimental cellular and animal models, arimoclomol ameliorates key degenerative and inflammatory features of IBM pathology. In a randomized, placebo-controlled safety and tolerability trial, arimoclomol (300 mg/day) was found to be safe and well tolerated in sIBM patients. There was a trend in favor of arimoclomol in secondary endpoints of muscle function and functional IBM scales.[6] If arimoclomol were found to be beneficial for the treatment of IBM, this would represent the only effective treatment for this otherwise progressive disease.

4 TRIAL OBJECTIVES AND PURPOSE

4.1 Objectives

4.1.1 Primary Objective

- To evaluate the efficacy of arimoclomol at a daily dosage of 1200 mg (400 mg t.i.d) compared to placebo in the treatment of sporadic IBM at 20 months.

4.1.2 Safety Objective

- To evaluate the safety and tolerability of arimoclomol at a daily dosage of 1200 mg (400 mg t.i.d.) compared to placebo in the treatment of sporadic IBM over 20 months.

4.2 Estimands

4.2.1 Primary Estimand

The primary estimand – “Treatment policy” is defined as follows:

> *Treatment difference of change from baseline in the IBMFRS instrument’s total score between arimoclomol and control at 20 months for all randomised patients regardless of exposure, adherence to randomised treatment and changes in standard of care*

The treatment policy estimand assesses the expected benefit on the IBMFRS instrument in a future population that results from patients being offered treatment with arimoclomol as add-on to standard-of-care as compared to standard-of-care alone after 20 months of follow-up.

Generalisation of this estimand depends among other things on the extent to which the standard-of-care provided in this trial reflects clinical practice and whether the adherence to trial product administration in this trial reflects the behaviour of the target population. Accordingly, data collected regardless of discontinuation of trial product or background therapy will be used to draw inference.

In line with the primary estimand, the term “missing data” will be used to cover data that are planned to be collected but are not present in the database. This implies that data that are missing due to death are considered missing and thus could meaningfully have been collected. The premise for using this counterfactual while-alive approach is that deaths are assumed relatively rare and unrelated to the disease. Details on how missing data are handled further and imputed are detailed in Section

4.2.2 Secondary Estimand

The secondary and supportive estimand – “Hypothetical” estimand, is defined as follows:

Treatment difference of change from baseline in the IBMFRS instrument's total score between arimoclomol and control at 20 months for all randomised and exposed patients if all patients adhered to treatment.

The hypothetical estimand assesses the benefit on the IBMFRS instrument that a future population would be expected to experience if the patients did not discontinue arimoclomol when compared to standard-of-care. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected efficacy of arimoclomol compared to standard-of-care for purposes of treating individual patients. Generalisation of this estimand depends among other things on the extent to which the adherence to trial product administration in this trial could reflect the behaviour of the target population. Accordingly, only data collected while patients were exposed to trial IMP will be used to draw inference.

5 OVERALL STUDY DESIGN

5.1 Description of the Study Design

The clinical study will be a Phase 2/3 randomized, double-blind, placebo-controlled international study in 150 patients with sporadic IBM followed for 20 months. Total duration of the study per patient is approximately 22 months including screening and the end of study phone call. In this study there will be two treatment groups of 75 patients each, i.e., 75 patients receiving arimoclomol 400 mg t.i.d and the remaining 75 patients receiving placebo. There will be approximately 11 sites in the United States and 1 site in the United Kingdom.

Arimoclomol will be administered at 400 mg orally three times a day in this study. Capsules are 200 mg so each patient will take 2 capsules three times a day. Every effort should be made to allow approximately 6 to 7 hours between dosing. As arimoclomol 100 mg PO TID was a well-tolerated dosage in our pilot study and 200 mg PO TID was well-tolerated for 1 year in a familial ALS study, and safety data support the use of 400 mg PO TID, and since the latter dosage is felt to be appropriate based on extrapolation from our animal VCP IBM model data, we will initiate participants on the 400 mg PO TID dosage or matching placebo. The main adverse events recorded in previous studies were mild to moderate gastrointestinal events.

If a patient experiences an intolerable adverse event, dosing may be interrupted and supportive therapy administered as required. Detailed description of the dose reduction is located in Section 7.7. The patient will be followed up as planned per protocol for adverse events recording. Every effort will be made to continue to follow up and evaluate all subjects enrolled in this study.

Upon completion of this study, qualified patients may enter an open-label extension study at their last treatment visit (Month 20).

5.2 Study Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the change from baseline to Month 20 in the Inclusion Body Myositis Functional Rating Scale (IBMFRS) total score.

5.2.2 Secondary Endpoints

Secondary endpoints of this study will involve objective endpoints that could translate into the functional strength abilities of these patients. The quadriceps muscles are targeted in this Phase 2/3 trial because of their preferential weakness in IBM and their contribution to gait impairment and falls.[52] There is a correlation between quadriceps muscle strength and function including the distance walked at the 2- and 6-minute walk tests and timed tests of stair climbing, standing from a chair, and stepping up on curbs. Subjects with the best-preserved quadriceps strength exhibited the highest IBMFRS scores.

Secondary efficacy endpoints will include changes from baseline to Months 12 and 20 in the following measures of strength and function:

- IBMFRS total score (Month 12)6 minute walk test with 2 minute distance captured
- Modified Timed Up and Go (mTUG)
- Muscle Strength Testing
    - Manual Muscle Testing (MMT)
    - Isometric Contraction Testing of bilateral quadriceps strength using the MicroFET
- Health Assessment Questionnaire (HAQ- DI)
- Grip strength using the Jamar device
- SF-36
- Falls and near falls
- Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)
- Clinician Global Impression of Severity (CGIS) and Clinician Global Impression of Change (CGIC)

5.2.2.1 Six Minute Walk Test

The distance an IBM patient can walk in 6 minutes will be assessed. Subjects will be instructed to walk down one side of the track and back along the opposite side as quickly and safely as possible for 6 minutes. Subjects will be allowed to take breaks as needed during the walking period, but timing will continue during breaks. The distance walked in meters will be recorded after 2 minutes and 6 minutes. Use of assistive device and the type of device during this test will be documented each time. Instructions for administration of the test are provided in the Clinical Evaluator's Manual.

5.2.2.2 Modified Time Up and Go

Patient's ability to get up from a chair allowing subjects to use their arms (since most with sIBM cannot perform the task without pushing off), walk 3 meters, turn around and walk back to the chair and sit down. The use of nearby walls, or assistance from a caregiver, will not be allowed. This test will be performed twice and the fastest time will be used in the data analysis. Instructions for administration of the test are provided in the Clinical Evaluator's Manual. This objective endpoint represents a skill that is one of the first things that patients lose. This also can be the most debilitating loss that they will endure. Losing this function greatly hinders their ability to transfer.

5.2.2.3 Muscle Strength Testing

Muscle testing will be performed by three different methods. The first method is by Manual Muscle testing. 24 number of muscles will be tested. This method is routinely performed

in a clinical setting and has been shown to be reliable (see the Clinical Evaluator's Manual).

The second method involves using the MicroFET hand myometer of quadriceps muscle. This is a hand-held device that allows the examiner to push against a muscle while the patient resist. Unlike the manual muscle test which provides a range, this device will provide an actual number. One muscle group will be tested bilaterally (i.e., quadriceps). Each muscle is tested twice while the patient is encouraged by the clinical evaluator (CE) to exert maximal effort. Record the two trials generated by the patient. Effort should be made to keep the variability down to 15% between the two trials (see the Clinical Evaluator's Manual).

The third strength method is the use of a Jamar Dynamometer that will measure grip strength. Two trials should be performed on each side (see the Clinical Evaluator's Manual).

5.2.2.4 Health Assessment Questionnaire

The health assessment questionnaire (HAQ-DI) is a self-report functional status (disability) measure based on the five patient-centered dimensions (death, disability, discomfort, drug toxicity and dollar costs). The HAQ domain of disability is assessed by the eight categories of dressing, arising, eating, walking, hygiene, reach, grip, and common activities. Discomfort is determined by the presence of pain and its severity.

5.2.2.5 Number of Falls and Near Falls

Falls are common events in the lives of IBM patients. We will record the number of falls and near falls every month.

5.2.2.6 SF-36

The SF-36 will be performed as described in Section 8.

5.2.2.7 Patient Global Impression of Severity and Change

The PGIS and PGIC will be performed as described in Section 8.

5.2.2.8 Clinician Global Impression of Severity and Change

The CGIS and CGIC will be performed as described in Section 8.

5.2.2.9 Safety Endpoints

The safety endpoints are as follows:

- Adverse events (AEs);
- Hematology;
- Clinical chemistry;
- Vital signs;
- Columbia Suicide Severity Rating Scale (C-SSRS)

Exploratory Endpoints

We will examine two exploratory endpoints for this study and an additional exploratory endpoint in a subset of patients:

- Population pharmacokinetics (POP PK) and exposure response analysis.
- Presence of [redacted]
- [redacted] (sub-study in selected sites only; in a subset of patients [see Appendix 3])

5.2.2.10 [redacted]

This endpoint is to establish the presence or absence of [redacted]. The discovery of the first [redacted] marker for IBM, targeting [redacted] represents an important advance.[53-55]

Using a commercial [redacted] to stain muscle tissue of IBM patients demonstrates that [redacted] immunoreactivity is predominantly located in rimmed vacuoles and areas of myonuclear degeneration.[53] [redacted] has been possibly linked to severity of disease. Preliminary findings from a 25 patient case series indicated that 72% were seropositive and suggested that these were more disabled [longer time to get up and stand (p=0.012); more assistive devices need (OR=23.00; p=0.007) and lower total MRC sum score (p=0.03)]. We need approximately 2 mL of blood for each sample.

5.2.2.11 Pharmacokinetics Assessments

The arimoclomol plasma concentration data will be merged with PK sampling times and used to create the population input file for use in a population PK modelling analysis. Subsequently, the relationship between the arimoclomol steady state exposure and the efficacy and tolerability of arimoclomol will be explored using a PK/PD modelling approach. We need approximately 1 mL of blood for each sample.

The plasma concentration values will be reported in the clinical trial report and the results will be used for population PK analyses. In addition to the population PK analysis an exposure response analysis, evaluating correlation between exposure of arimoclomol and e.g. change in IBMFRS total score, will be performed. A separate modelling analysis plan will be issued before DBL and results will be reported separately.

5.2.2.12 Biobanking

Blood will be drawn for biobanking for future potential tests. Blood samples will be obtained, stored, and shipped as detailed in the Central Laboratory Manual.

6 STUDY ENROLLMENT AND WITHDRAWAL

6.1 Trial Conduct

This clinical trial will be conducted in compliance to this protocol, the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

6.2 Inclusion Criteria

Study subjects must meet all of the following criteria which must be documented in the study site source documents:

1. Meet any of the European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011 categories for IBM.[1] (see Appendix 1)
2. Demonstrate being able to arise from a chair without support from another person or device
3. Able ambulate at least 20 ft/6 meters with or without assistive device. Once arisen from the chair, participant may use any walking device, i.e. walker/frame, cane, crutches, or braces. They cannot be supported by another person and cannot use furniture or wall for support.
4. Age at onset of weakness > 45 years
5. Body weight of $\geq$ 40 kg
6. Able to give informed consent.

6.3 Exclusion Criteria

Study subjects must not meet any of the following criteria which must be documented in the study site source documents:

1. History of any of the following excludes subject participation in the study: chronic infection particularly HIV or Hepatitis B or C; cancer other than basal cell cancer less than five years prior; or other chronic serious medical illnesses.
2. Presence of any of the following on routine blood screening: WBC<3000; platelets < 100,000; hematocrit < 30%; BUN > 30 mg/dL; creatinine > 1.5 x upper limit of normal; symptomatic liver disease with serum albumin < 3 g/dL.
3. History of most recent creatine kinase >15x the upper limit of normal without any other explanation besides IBM.
4. History of non-compliance with other therapies.
5. Use of testosterone except for physiologic replacement doses in case of androgen deficiency. Participants must have documented proof of the androgen deficiency.
6. Coexistence of any other disease that would be likely to affect outcome measures.
7. Drug or alcohol abuse within past three months. Patient has recent history (within 6 months before Screening) of chronic alcohol or drug abuse which may compromise the patient's safety or ability to participate in study activities. Cannabis for IBM symptoms will be allowed (where legal).
8. Participation in a recent drug study in the last 30 days prior to the screening visit or use of a biologic agent less than 6 months prior to the screening visit.

9. Women who are lactating or pregnant, or sexually active female subjects of child-bearing potential* intending to become pregnant or unwilling to use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. Sexually active males with female partners of child-bearing potential* unwilling to use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication unless surgically sterile (vasectomy).

** Non child-bearing potential is defined as post-menopausal (minimum of 12 months with no menses and follicle-stimulating hormone in the post-menopausal range) or sterilisation (hysterectomy, oophorectomy, or bilateral tubal ligation).*

*** Highly effective methods of contraception include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomised partner.*
According to the recommendations from the Clinical Trial Facilitation Group (CTFG, 2014), sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual intercourse during the trial until 1 month after the last dose of trial medication (for female subjects of child-bearing potential) and for 3 months after the last dose of trial medication (for male subjects with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10. Participants taking >7.5mg prednisolone or equivalent or participants on intravenous immunoglobulin (IVIg) or other immunosuppressants within the last 3 months. Topical, nasal, and ocular corticosteroids are allowed unless they are being widely applied or the severity of the underlying condition makes them unsuitable in the Investigator's opinion. Local steroid injections are allowed.
11. Clinically significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 times the upper limit of normal [ULN] for alanine aminotransferase combined with bilirubin ≥2 times the ULN; symptomatic liver disease with serum albumin < 3 g/dL; or creatinine ≥1.5 times the ULN). Laboratory tests may be repeated once at screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist, or to rule out laboratory error.

6.4 Strategies for Recruitment and Retention

The sample size will be 75 participants per group (150 total).

There will be approximately 11 sites within the US and 1 site within the UK. The UK anticipates recruiting approximately 50 patients and each site within the US believes that they can recruit up to 10 patients per site.

Each site involved in this study has a large database of IBM patients and since there are no other current drug treatment trials involving IBM patients, we anticipate that each site would be able to recruit their patients within 1 year of start up. The study is currently listed on clinicaltrials.gov.

If necessary, letters to neurologists within each sites region will be sent if enrollment is slow. The Myositis Association will be contacted to assist with recruitment.

6.5 Participant Withdrawal or Termination

6.5.1 Reasons for Withdrawal or Termination

The patient will be advised in the ICF that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's, or the Sponsor's discretion at any time. In addition, early withdrawal may occur for any of the following reasons:

- Patient requests (withdrawal by subject)
- Investigator decides that it is in the patient's interest (physician decision)
- Serious AE that is probably or definitely related to the study medication
- Death
- Failure to meet eligibility criteria
- Lost to follow-up
- Significant protocol violation
- Breaking of the blind
- Pregnancy
- Commencing systemic treatment with prednisolone >7.5 mg or equivalent (except if short course [up to 4 weeks] administration not related to IBM e.g. due to an asthma attack), IVIg, or other immunosuppressants
- Commencing other experimental or prohibited treatments
- Study terminated by Sponsor
- Other

6.5.2 Handling of Participant Withdrawals or Discontinuation of Study Treatment

In the event that the patient permanently discontinues study treatment, the patient will be encouraged to continue attending the protocol-specified study visits for continued assessments.

According to the FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (64), IMP must be permanently discontinued in the case of the following:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and bilirubin >2 x ULN or International Normalised Ratio (INR) >1.5)

- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Re-challenge in case of increased transaminases:

If in the Investigator's judgement, a temporary halt in IMP is instituted because of elevated transaminases, a re-challenge must not occur if the patient had the following:

- ALT or AST > 5 x ULN
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALT or AST > 3 x ULN AND bilirubin >2 x ULN

IMP must also be discontinued for subjects with elevated transaminases where close observation (repeated laboratory tests) is not possible, see Section 6.5.2

In the event that the patient drops out of the study or is withdrawn from the study, the end of study/discontinuation page in the patient's case report form (CRF) should be completed. On the end of study/discontinuation page, the Investigator (or designee) should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal. Withdrawn patients will not be replaced.

If a patient is unable to return to the center, a phone call will be made to the patient in order to complete assessments and retrieve any outstanding data. All attempts to make contact with the patient should be documented in source notes. In the event of a loss to follow up, information about the patient will be sought from the family or family physician.

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

6.5.2.1 Premature Termination of the Study

The Scientific Steering Committee and the Sponsor may jointly decide to terminate the trial at any time for any reason.

The Sponsor will terminate the study if the Sponsor determines that its investigational drug presents an unreasonable and significant risk to patients. Time permitting, the Sponsor will notify the Steering Committee and involve the Steering Committee in its decision.

The Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) may recommend to the Sponsor, and the regulatory authorities may require from the Sponsor, that the study is terminated for reasons pertaining to efficacy, safety or quality of the investigational product (arimoclomol). A decision to prematurely terminate the study will be binding to all Site Investigators of all study centers. IECs/IRBs and regulatory authorities will be informed about the reason and timing of such termination according to the applicable laws and regulations.

6.5.2.2 Premature Discontinuation of Study Participation at Individual Centres

The Sponsor and the Scientific Steering Committee may jointly decide to discontinue this study in one particular or several study centre(s) for reasonable cause, including but not limited to one of the following reasons:

- Non-compliance with GCP and/or regulatory requirements.
- Inability of the site to be activated in a timely fashion.
- Centre cannot recruit an adequate number of patients in a timely fashion.
- False documentation in the CRF, either deliberately or due to carelessness.
- Inadequate co-operation with the Sponsor or its representatives.
- The Investigator requests closure of his/her study centre.

If the study participation is prematurely discontinued in one or more study centers, site Investigators must inform their patients and take care of appropriate follow-up and further treatment of the patients. Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) and regulatory authorities will be informed about reason and time of discontinuation according to the applicable laws and regulations.

For patients who leave during the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

6.5.2.3 Regular Termination of Study

End of study will be 22 months after recruitment of the last patient (1 month screening period, 20 months treatment, 1 month follow-up), or earlier if all patients have completed or withdrawn from the study prior to this time point.

Within 90 days of the end of a clinical study, the Sponsor will notify IECs/IRBs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

If the study has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

7 STUDY TREATMENT

7.1 Study Agent(s) and Control Description

In this parallel-group randomized trial, subjects who meet trial entry criteria will be randomly assigned in a 1:1 ratio to arimoclomol or placebo. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IMP to randomization numbers. The randomization numbers will be assigned sequentially as subjects are entered into the trial.

When all screening procedures are completed and the site investigator believes that the subject is eligible, the site will contact the KUMC project manager (or delegate) who will confirm completeness of the eCRF data prior to randomization. If the data is confirmed as complete, the KUMC project manager (or delegate) will perform the randomization before the baseline visit. A randomization confirmation email will automatically be generated to the study site staff and management team. Study medication bottle numbers to be dispensed at the baseline visit will already have been distributed to the site in advance of randomization.

7.2 IMP Manufacturing

The drug substance will be manufactured and released by Patheon (US) and will be utilized to prepare hard capsules of arimoclomol citrate containing standard compendial excipients. Arimoclomol capsules are manufactured by Patheon (FR). The IMP is labelled, packed and released according to the IMPD.

7.3 Formulation, Appearance, and Packaging

Arimoclomol is an odourless, crystalline powder of white or off-white colour supplied in hard capsules of 200 mg. For each strength, capsule fill will be a powder mix of active pharmaceutical ingredient (API), with the remainder made of [redacted] and [redacted]. Arimoclomol is formulated into size “0”, white hard capsules for oral administration. For this Phase 2/3 clinical trial, capsule strength is 200 mg.

The placebo capsule is visually indistinguishable from the arimoclomol capsule in size and appearance. The placebo of the same size (size 0) will be presented with an identical weight capsule fill in identical white hard capsules and packaged and labelled as described for arimoclomol. The excipient composition, texture, appearance, solubility, smell and flavour of the placebo are carefully matched to mask the identity of the active capsule (arimoclomol). In the placebo formulation, the API is exchanged to Bitrex® (denatonium benzoate) as placebo flavour masking.

The capsules are packed in high density polyethylene (HDPE) bottles each containing 84 capsules.

7.4 Product Storage and Stability

Clinical batches of active and placebo capsules will be placed in a stability study in accordance to International Conference on Harmonization (ICH) stability program. The stability testing will be performed on packaged product in bottles as applicable.

In-use stability data following pre-mixing of the capsules contents into a suitable beverage or soft food vehicle (e.g. water, apple juice, and yogurt) as well as feeding-tube recovery are documented.

Based on the available stability data, the IMP capsules are recommended to be stored at USP controlled room temperature, i.e., store at 15º to 25ºC with excursions permitted between 2º and 30ºC.

7.5 Preparation

Arimoclomol citrate is a highly soluble compound with an aqueous solubility of 14 g/100 mL. Arimoclomol is formulated in size “0”, white hard capsules for oral administration.

All the excipients are listed in the FDA’s inactive ingredients database.

Arimoclomol capsules are available as oral capsules in strengths of 25 mg, 50 mg, 100 mg, and 200 mg, but only 200 mg capsules will be used for this study. The dose in the Phase 2/3 clinical trial is 400 mg t.i.d.

7.6 Dosing Route and Regimen

The IMP (arimoclomol and placebo) may be dispensed only by the site Investigator or by a staff member assigned by the site Investigator, as appropriate. The IMP will be dispensed to the patient during site visits or may be shipped to the patient’s house (as appropriate).

The contents of the hard capsules can be dispersed in 10-30 mL (i.e. 1-2 tablespoons) of water, milk or juice or sprinkled on foods like apple sauce, or yogurt etc. to promote dose compliance.

In aqueous dispersed state, the capsule content can be administered through a gastric tube. The tube should be flushed with 5 mL of water.

7.7 Starting Dosage, IMP interuption, rechallenge and permanent discontinuation

Dosing will start at 400 mg 3 times a day. If a patient experiences an intolerable adverse event, dosing may be interrupted and supportive therapy administered as required. All dosing interruptions must be discussed with the contract research organization (CRO)’s medical monitor.

An interruption of up to 4 weeks (calculated from the first day of interruption) is permitted following discussion with the CRO’s medical monitor prior to resuming IMP. The interruption of the dose should be as short as possible.

If the patient experiences the same intolerable adverse event after re-challenge with the full dose of IMP, the dose can be reduced to half, i.e., 200 mg t.i.d., following discussion

with the CRO's medical monitor. The patient must continue this dose for the remaining part of the study. If this dose is not tolerated, the IMP must be discontinued permanently. This sequence of events can be implemented only once for intolerable AEs within a given organ/body system. If the patient experiences a different intolerable adverse event within a different organ/body system, this sequence of events can be repeated for that AE.

According to the FDA Guidance for Industry on Drug-Induced Liver Injury (DILI) (64), IMP must be permanently discontinued under circumstances related to elevated transaminases. IMP must also be discontinued for subjects with elevated transaminases where close observation (repeated laboratory tests) is not possible, see Section 6.5.2

If in the Investigator's judgement, a temporary halt in IMP is instituted because of elevated transaminases, a re-challenge must not occur if criteria described in Section 6.5.2 are met.

7.8 Duration of Therapy

Patients will receive the study medication for 20 months.

7.9 Investigational Product Accountability

Site Investigator or pharmacist, or an approved representative, should maintain records of the product's delivery to the study center, the inventory at the centre, the administration to each patient, and will ensure that all investigational products are stored in a secure, limited access area. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study patients.

A temperature log should also be kept and should be made available when the monitors arrive on site or does remote monitoring.

Investigators should maintain records that document adequately that the patients were administered the dose specified by the Protocol and reconcile all investigational product(s) received from the Sponsor.

To ensure adequate records, all study treatments will be accounted for on an ongoing basis throughout the study in drug accountability forms at the study centre.

Subjects will receive study medication at clinic visits at baseline, Months 1, 4, 8, 12 and 16. Subjects will use a medication log and will be instructed to return all unused study medication at each clinic visit. Compliance will be assessed by review of the medication log at each visit and by documentation of unused study medication. A subject who is not adherent (taking less than 80% of assigned capsules) will be counseled at each visit on the importance of taking IMP as instructed.

8 STUDY PROCEDURES AND SCHEDULE

8.1 Study Specific Procedures

Please refer to the Schedule of Events in Table 2.

8.1.1 Consent

Patients will be given opportunity to read, ask questions, have those questions answered and sign the consent before any study procedures are performed. The consenting procedure must be documented.

For competent trial subjects who have lost dexterity in the hands and cannot personally sign and date the informed consent form, an impartial witness signature may be used to document that the participant understands the study, the consent process, and has consented to continue to participate in the trial (if permitted by local regulations).

8.1.2 Inclusion/Exclusion/Eligibility/Screen Failure

Each patient must satisfy inclusion/exclusion criteria and must be eligible for the study before they can be randomized. Once a patient is randomized eligibility checks will not be repeated at the baseline visit.
If a patient is found not to be eligible due to exclusion criteria # 2, 5, or 10, the specific eligibility criterion can be reassessed and out-of-range laboratory results can be redrawn within the 30-day screening window. For subjects outside of the screening window, rescreening is allowed only once and only if approved by the medical monitor. Rescreening will be conditional on medical monitor approval if it is considered to be due to one of the following three reasons:

- Subject failing to satisfy exclusion criteria # 2, 5, or 10 which according to the opinion of the medical monitor is for an unrelated or reversible reason
- Out of window baseline visit
- If a concurrent medical condition in the opinion of the investigator requires initiation of treatment or optimization of treatment. The subject can be rescreened when the condition is stabilized.

8.1.3 Medical History Including IBM history

All past medical history that might affect the results of the study, such as muscle, bone, and degenerative disease that might affect performance on the outcome measures, must be recorded. Information specific to IBM including date of onset and site of onset must be obtained.

8.1.4 Physical Examination

A general physical examination must be performed by a physician; in countries where accepted, this task can be delegated when documented on a delegation log.
At months 3, 5 and 6 the physical examination may be conducted in a short-form. As a minimum, the examination must include assessments of right upper quadrant pain or tenderness and rash.

8.1.5 IBM Functional Rating Scale

The IBMFRS is a quickly administered (10-minute) ordinal rating scale used to determine participants' assessment of their capability and independence. It includes 10 measures (swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, changing position from sitting to standing, walking, and climbing stairs), graded on a Likert scale from 0 (being unable to perform) to 4 (normal). The sum of the 10 items gives a value between 0 and 40, with a higher score representing less functional limitation.

8.1.6 Patient Global Impressions of Severity and Change

The Patient Global Impression of Severity (PGIS) is a patient-reported assessment of the impact of IBM on a patient's ability to complete activities of daily living right now. The scale ranges from 'none' to 'very mild,' 'mild,' 'moderate,' 'severe,' and 'very severe' impact. The Patient Global Impression of Change (PGIC) is an assessment by the subject of self-perceived change in ability to conduct daily activities since the start of study medication. The scale ranges from 'very much worse' to 'much worse,' 'a little worse,' 'no change,' 'a little improved,' 'much improved,' and 'very much improved'.

8.1.7 Clinician Global Impressions of Severity and Change

The Clinician Global Impression of Severity (CGIS) is a clinician-reported assessment of the severity of the patient's IBM symptoms right now. The scale ranges from 'none' to 'very severe'. The Clinician Global Impression of Change (CGIC) is an assessment by the clinician of change in the patient's IBM since the start of study medication. The scale ranges from 'very much worse' to 'very much improved'.

8.1.8 Muscle Strength Testing

Muscle testing will be performed by three different methods. The first method is by Manual Muscle testing. 24 muscles will be tested. This method is routinely performed in a clinical setting and has been shown to be reliable.

The second method involves using the MicroFET hand myometer. This is a hand-held device that allows the examiner to push against a muscle while the patient resists. Unlike the manual muscle test which provides a range, this device will provide an actual number. One muscle group will be tested bilaterally (i.e., quadriceps). Each muscle is tested twice while the patient is encouraged by the Clinical Evaluator (CE) to exert maximal effort. The maximum force generated by the patient from the two trials is used for each muscle group.

The third strength method is the use of a Jamar Dynamometer that will measure grip strength. The maximum force generated by the patient from the two trials is used for each muscle group.

8.1.9 Modified Timed Up and Go (mTUG)

We will measure the patient's ability to get up from a chair allowing participants to use their arms (since most with sIBM cannot perform the task without pushing off), walk 3 meters, turn around and walk back to the chair and sit down. The use of nearby walls,

or assistance from a caregiver is not allowed. This test will be performed twice and the fastest time will be used in the data analysis.[52,56]

8.1.10 6 Minute Walk Test with 2 Minute Distance Captured

We will assess the distance IBM participants can walk in 6 minutes. Participants will be instructed to walk down one side of the track and back along the opposite side as quickly and safely as possible for 6 minutes. Participants will be allowed to take break as needed during the walking period, but timing will continued during breaks. Time to complete each 50-meter lap and distance walked in meters will be recorded after 2 minutes and 6 minutes. We will capture use of assistive devices during the test.

8.1.11 Falls Diary

Each subject will record the number and date of falls and near falls within each month period.

8.1.12 Health Assessment Questionnaire – Disability Index (HAQ- DI)

This is a self-report functional status (disability) measure based on the five patient-centered dimensions (death, disability, discomfort, drug toxicity and dollar costs).[57-58]

8.1.13 Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS), will be administered to the subject by study personnel at the screening visit using the “baseline/screening” version of the scale. The “since last visit” version will be administered at all other clinic visits.

8.1.14 Vital Signs

Vital signs, including weight, heart rate, respiratory rate, and sitting blood pressure will be measured after the subject has been in a sitting position for 5 minutes. Temperature will also be measured. Any clinical significant abnormality must be reported as an AE.

8.1.15 ECG

A standard 12-lead ECG will be performed after the subject has been lying down for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording. The ECG interpretation will be recorded in the subject’s eCRF. Any abnormality at screening will be listed as medical history; any subsequent clinically significant abnormality must be reported as an AE.

8.1.16 SF-36

The Short Form-36 Health Survey is a 36-item, patient-reported survey of health. The SF-36 is a measure of health status.

8.1.17 [redacted]

Samples of 2 mL of serum will be collected to obtain [redacted] levels. Serum samples will be obtained, frozen at -70 degrees Celsius, and shipped.

8.1.18 Biobanking

We will collect approximately 12 mL of blood at screening and approximately 6 mL of blood at Months 4, 8, 12, and 20 for potential future testing.

8.1.19 POP PK

Samples of blood will be drawn as specified in the laboratory manual at month 1 pre-dose and then 0.5 hours (+ 60 min) post-dose, and month 8 pre-dose and then 1.5 hours (+ 60 min) post-dose. A total of 4 samples per subject will be drawn; 2 samples at Month 1 and 2 samples at Month 8. Patients will be asked to confirm the mode of administration (as per section 7.6) of the last dose taken at home before the POP PK blood draw.

8.1.20 Laboratory Procedures/Evaluations

For each in-person visit, except for the Baseline visit, the following lab procedures will be performed:

Hematology with differentials	hemoglobin; hematocrit; mean corpuscular volume (MCV); red blood cells (RBC/erythrocytes); white blood cells (WBC/leukocytes); and differential count (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% and absolute count], and platelets)
Biochemistry	albumin; alkaline phosphatase; alanine aminotransferase (ALT/SGPT); aspartate aminotransferase (AST/SGOT); bilirubin (total); calcium; chloride; cholesterol; creatine kinase); creatinine; gamma-glutamyl transferase (GGT); glucose (random); iron; lactate dehydrogenase (LDH); phosphate; potassium; protein total; sodium; triglycerides; BUN; uric acid
Other	cystatin C

A urine pregnancy test will be performed on women of childbearing potential before the study medication is given to them at baseline and at each visit.

All laboratory results must be signed and dated by the physician in a timely manner. All abnormal results will be classified as either clinically significant or not clinically significant.

All clinically significant abnormal values must be recorded as medical history or AEs, as appropriate. All of the above mentioned laboratory tests will be performed by a central laboratory.

If the subject cannot attend the trial site for specific laboratory follow-up, the analyses may be conducted at a local laboratory. For guidance on follow-up of specific laboratory abnormalities, see section 9.6

8.1.20.1 Specimen Preparation, Handling and Shipment

All laboratory samples will be handled and shipped as per the Central Laboratory Manual.

8.2 Study Schedule

This study is co-funded by a 4-year FDA-OPD grant and Orphazyme. We anticipate approximately 15 months of active screening and enrollment, and 21 months of treatment and follow-up.

The planned sequence and maximum duration of the trial periods will be as follows:

1. Screening: up to 1 month
2. Treatment: 20 months
3. Post-treatment Follow-up Call: 1 month after last dose of IMP

The maximum treatment duration for each subject is approximately 20 months.

The maximum trial duration for each subject is approximately 22 months.

Following the screening and baseline visits, Visits 3 to 7 are to occur every 30 days (± 7 days) and the remaining visits are to occur every 60 days relative to baseline (± 7 days). In-person follow up visits at the trial site are to occur at Months 1, 2, 3, 4, 5, 6, 8, 12, 16, and 20. Phone calls will be made at Months 10, 14, 18, and 21. If a patient must stop the trial medication for any reason, every effort will be made to have the patient participate in each subsequent visit as scheduled.

8.2.1 Screening (30 Day Window) (Visit 1)

The subject must be screened within 30 days before enrollment in the trial. The following procedures will be performed at screening:

- Obtain written informed consent and/or assent.
- Assess inclusion/exclusion criteria.
- Collect demographic information.
- Record IBM history and medical history, including current therapies (e.g., prescription and nonprescription medications).
- Perform a physical examination.
- Measure vital signs, including weight, pulse, sitting blood pressure, respiratory rate, and temperature.
- Perform a 12-lead ECG.
- Collect blood for safety laboratory tests, anti-[redacted] levels, and biobanking.
- Complete the C-SSRS “baseline/screening” (lifetime) assessment.

8.2.1.1 Randomization

The site investigator will review and sign off on all inclusion and exclusion criteria and safety laboratory tests prior to randomization. Completeness of eCRF and safety laboratory data will be reviewed by the KUMC project manager (or delegate) before randomization can occur as detailed in Section 7.

8.2.2 Baseline (Visit 2, Day 1)

The following procedures will be performed at Visit 2 (baseline):

- Measure vital signs, including weight.
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Record concomitant medications and concomitant therapies.
- Assess and record AEs occurring since signing of informed consent.
- Complete the PGIS, IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, grip assessments, 6 minute walk test with 2 minute distance, HAQ-DI, SF-36, and CGIS.
- Administer the first dose of IMP and observe for 1 hour after the dose.
- Dispense IMP for the initial one-month period, and give the patient instructions regarding dosing schedule and trial requirements.
- Provide the subject with a falls diary.
- Remind patient not to take the morning dose of the study medication on the day of the Month 1 visit (to allow for pre-dose PK blood sampling).

8.2.3 Ongoing Treatment Visits (Visits 3 to 13, Months 1 to 18)

8.2.3.1 Months 1 and 2

The following procedures will be performed at the site visits at Months 1 and 2:

- At Month 1 only, to enable a pre-dose PK sample, the patient must not have taken study medication approximately 8 hours prior to the site visit.
- Measure vital signs, including weight.
- Perform a physical examination.
- Collect blood for clinical safety laboratory tests and (at Month 1 only) for PK (pre-dose).
- At Month 1 only, the patient takes dose of study medication in the clinic.
- At Month 1 only, collect blood for PK 0.5 hours post-dose as per protocol section 8.1.19.
- Record concomitant medications and concomitant therapies.
- Assess and record AEs occurring since the last evaluation. Follow up ongoing AEs.
- Complete the IBMFRS.
- Complete the C-SSRS (“since last visit” assessment).
- Perform a urine pregnancy test for female subjects of childbearing potential.

- At Month 1 only, collect empty IMP packaging and unused IMP, and dispense additional IMP.
- Collect and review the falls diary and give the subject a new falls diary.

8.2.3.2 Months 3, 5, and 6

The following procedures will be performed at the site visits at Months 3, 5 and 6:

- Collect blood for clinical safety laboratory tests
- Record concomitant medications and concomitant therapies.
- Perform a physical examination.
- Assess and record AEs occurring since the last evaluation. Follow up ongoing AEs.
- At Month 3 and 6 only, complete the IBMFRS
- Complete the C-SSRS ("since last visit" assessment).

8.2.3.3 Months 4, 8, 12, and 16

The following procedures will be performed at the site visits at Months 4, 8, 12, and 16:

- At Month 8 only, to enable a pre-dose PK sample, the patient must not have taken study medication approximately 8 hours prior to the site visit.
- Measure vital signs, including weight.
- Perform a 12-lead ECG (Month 12 only).
- Perform a physical examination.
- Collect blood for clinical safety laboratory tests, anti-[redacted] levels (Month 12 only), biobanking (Months 4, 8, and 12 only), and PK (Month 8 only; pre-dose).
- At Month 8 only; the patient takes dose of study medication in the clinic.
- At Month 8 only; collect blood for PK 1.5 hours post-dose as per protocol section 8.1.19.
- Record concomitant medications and concomitant therapies.
- Assess and record AEs occurring since the last evaluation. Follow up ongoing AEs.
- Complete the PGIS, PGIC, IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, grip assessments, 6 minute walk test with 2 minute distance, HAQ-DI, SF-36, CGIS, and CGIC.
- Complete the C-SSRS ("since last visit" assessment).
- Collect empty IMP packaging and unused IMP, and dispense additional IMP.
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Collect and review the falls diary and give the subject a new falls diary.

8.2.3.4 Months 10, 14, and 18

The following procedures will be performed at the telephone visits at Months, 10, 14, and 18:

- Record concomitant medications and concomitant therapies.
- Assess and record AEs occurring since the last evaluation.
- Complete the IBMFRS.
- Ensure the subject has sufficient IMP and arrange for additional IMP supplies if needed.
- Review the falls diary.

8.2.4 Final In-person Study Visit and Follow-Up Phone Call

The following procedures will be performed at the final in-person trial visit at Month 20:

- Measure vital signs, including weight.
- Perform a 12-lead ECG (Month 20 only).
- Perform a physical examination.
- Collect blood for safety laboratory tests, anti-[redacted] levels, and biobanking.
- Record concomitant medications and concomitant therapies.
- Assess and record AEs occurring since the last evaluation.
- Perform a urine pregnancy test for female subjects of childbearing potential.
- Complete the PGIS, PGIC, IBMFRS, MMT, MVICT of quadriceps and grip, mTUG, grip assessments, 6 minute walk test with 2 minute distance, HAQ-DI, SF-36, CGIS, and CGIC.
- Complete the C-SSRS (“since last visit” assessment).
- Collect empty IMP packaging and unused IMP.
- Collect and review the falls diary.

Upon completion of this study, qualified patients may provide informed consent and enter an open-label extension study at the Month 20 visit. Assessments recorded at this visit will also constitute the first assessments of such open-label extension study.

The following procedures will be performed at the final telephone visit at Month 21:

- Record updates to any concomitant medications or therapies that were ongoing at the previous visit.
- Record updates to any AEs that were ongoing at the previous visit.
- Record any new SAEs.

8.2.5 Early Termination Visit

If the patient wishes to withdraw from the study and they do not wish to continue in the study visits (see Section 6.5.2), you must bring them in for the Month 20 (Visit 14) study procedures. This will need to be followed by the visit 15 (30 day post-visit) phone call.

8.2.6 Unscheduled Visits

Unscheduled visits to evaluate potential adverse events can occur at any time. Vital signs, physical examinations, safety laboratory, C-SSRS, adverse events and concomitant medications will be collected during this visit. If this visit is greater than 1 week before their regularly scheduled appointment, they must also attend the regularly scheduled appointment. Unscheduled visits that are solely for the purpose of refilling medication do not require any of the safety assessments.

8.2.7 Exceptional Circumstances Preventing Patient From Attending In-Person Visits

In the exceptional circumstance that a patient cannot attend a scheduled or an unscheduled visit at the site information about adverse events, concomitant medications and IBMFRS can be obtained via telephone. Such an exceptional circumstance should be discussed with the CRO's medical monitor.

Table 2: Schedule of Events

Visit #	1	2	3	4	5	6	6a	7	8	9	10	11	12	13	14	15
Month	**-1 (Sc)**	**0 (Base)**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20 ‡**	**21**
Consent	X															
Eligibility	X															
Medical History	X															
IBM History	X															
Vital signs, including weight	X	X	X	X		X			X		X		X		X	
Physical Exam	X		X	X	X	X	X	X	X		X		X		X	
Safety Labs**	X		X	X	X	X	X	X	X		X		X		X	
Urine Preg***		X	X	X		X			X		X		X		X	
Blood for [redacted] levels	X										X				X	
Blood for biobanking	X					X			X		X				X	
POP PK			X						X							
ECG	X										X				X	
Randomization****	X															
Dispensing of Medication		X	X			X			X		X		X			
Return of Medication			X			X			X		X		X		X	
PGIS/PGIC		X				X			X		X		X		X	
C-SSRS	X		X	X	X	X	X	X	X		X		X		X	
Muscle Testing (MMT, MVICT)		X				X			X		X		X		X	
6 min walk test		X				X			X		X		X		X	
SF-36		X				X			X		X		X		X	
HAQ-DI		X				X			X		X		X		X	
Falls diary		X	X	X		X			X		X		X		X	
Grip		X				X			X		X		X		X	
IBMFRS		X	X	X	X	X		X	X	X	X	X	X	X	X	
mTUG		X				X			X		X		X		X	
CGIS/CGIC		X				X			X		X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*

Phone visits are shaded gray.

Note: Visit windows for all visits are ± 7 days relative to baseline.

* = Only stop dates for ongoing AEs and new SAEs

** = Full Safety Labs: See section 8.1.20 *Laboratory Procedures/Evaluations*

*** = Urine pregnancy prior to dispensing study medication

**** = Randomization procedure see section 7.1

‡ = Upon completion of this study, qualified patients may provide informed consent and enter an open-label extension study at the Month 20 visit. Assessments recorded at this visit will also constitute the first assessments of such open-label extension study.

8.3 Concomitant Medications, Treatments, and Procedures

Concomitant medication use, including over-the-counter supplements, will be documented throughout the study. The entry will include the dose, regimen, route, indication, and dates of use. Antioxidants and vitamins will be allowed. There may be soreness from the strength and functional tests that the patients must undergo.

Concomitant procedures (e.g. ultrasound investigation of the liver) must be recorded in the CRF.

8.4 Precautionary Medications, Treatments, and Procedures

Arimoclomol is an in vitro inhibitor of the OCT2, MATE-1, and MATE-2K transporters and consequently may inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an in vitro substrate of the MATE-1 and MATE-2K transporters. Arimoclomol undergoes renal tubular secretion, and concomitant treatment with drugs that are MATE-1 or MATE-2K inhibitors may therefore lead to increased exposure of arimoclomol. Consequently, the concomitant use of cationic drugs that are significantly eliminated by tubular secretion as well as drugs that are MATE-1 or MATE-2K inhibitors should be administered with caution. These include, but are not limited to, amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin, dofetelide, trimethoprim, quinidine, verapamil, levofloxacin, ciprofloxacin, moxifloxacin, pyrimethamine, and ondansetron.

Additionally, in vitro studies show that arimoclomol is a direct inhibitor of CYP2D6 and may potentially cause increase in exposure of co-administered medications that are substrates of CYP2D6 when arimoclomol is dosed at 400 mg t.i.d.

Since, the magnitude of the potential increase cannot be predicted from in vitro data caution is advised if arimoclomol is co-administered with medicinal products that are metabolised by CYP2D6. This may for examples be relevant for class I anti-arrhytmics, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI's) particularly if they are known to be sensitive and moderate sensitive CYP2D6 substrates and/or have a narrow therapeutic index.

The product information for co-administered medicinal products should be consulted for guidance on concomitant treatment with a CYP2D6 inhibitor as dose adjustment of the CYP2D6 substrate may be appropriate. For compounds metabolised by CYP2D6 the dose may be reduced and for pro-drugs that are converted to the active compound by CYP2D6 the dose may be increased to ensure efficacy.

Animal studies have indicated a possible interaction with furosemide (additive effect) and enalapril (decreased effect), both at high doses, and consequently concomitant dosing should be done with caution.

8.4.1 Prohibited Medications, Treatments, and Procedures

The following medications are prohibited during the study and for specified durations prior to enrollment as noted in the exclusion criteria:

- Use of testosterone except as allowed in the exclusion criteria.
- Cannabis except as allowed in the exclusion criteria.
- Prednisone, IVIg, or other immunosuppressants except as allowed in the exclusion criteria. A short course [up to 4 weeks] of systemic treatment with prednisolone >7.5 mg or equivalent is allowed for conditions not related to IBM (e.g. due to an asthma attack). Topical, nasal, and ocular corticosteroids are allowed unless they are being widely applied or the severity of the underlying condition makes them unsuitable in the Investigator's opinion. Local steroid injections are allowed.
- Other experimental treatments

Should there become a medication, treatment, or procedure that is either precautionary or prohibited, all patients will be notified immediately. IRB/IEC's will be notified as soon as possible; also include any IMP or any product not approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration.

8.4.2 Prophylactic Medications, Treatments, and Procedures

There may be soreness from the strength and functional tests that the patients must undergo. They may take normal prophylactic medications, treatments or procedures to ease the soreness.

8.4.3 Rescue Medications, Treatments, and Procedures

Currently there are no rescue medications, treatments and procedures to treat IBM.

8.4.4 Participant Access to Study Drug At Study Closure

Upon completion of this study, qualified patients may provide informed consent and enter an open-label extension study.

9 ASSESSMENT OF SAFETY

9.1 Adverse Events

9.1.1 Adverse Event Definition

An AE is defined as: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can also refer to an untoward response to the administration of the IMP, but can also occur as a result of the protocol-required procedures or be unrelated to both and include worsening of pre-existing conditions, for example.

AEs include the following:

- Suspected adverse medication reactions;
- Reactions from medication overdose, abuse, sensitivity, or toxicity;
- Apparently unrelated illnesses, including the worsening of a pre-existing illness;
- Injury or accidents;

Note: If a documented medical condition is known to have caused the injury or accident, only the accident should be reported as an AE;

- New or aggravated clinically relevant abnormal medical finding at a physical examination as compared with previous assessments;
- Laboratory abnormalities or other abnormal assessments (e.g. physical examination, vital signs, ECG) that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.

9.1.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death;

  Note: Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome. In reports of death due to “Disease Progression”, where no other information is provided, the death will be assumed to have resulted from progression of the disease under investigation.

  All deaths occurring on the study or patient withdrawal must be reported.
- Is life-threatening;

  A life-threatening event places the patient at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient hospitalization or prolongation of existing hospitalization;

  Note: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether other events meet the serious criteria, the event is to be considered serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity;

  Note: The term "significant disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, hospital, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect;

- Is an important medical event(s) that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in such circumstances.

9.2 Recording and Reporting of Adverse Events

All AEs and SAEs, as defined above, encountered during the clinical study will be reported in the appropriate section of the CRF. Information will include the following:

- Duration of the AE (onset/resolution dates);
- Relationship to the IMP (refer to Section 9.2.2);
- Severity (refer to Section 9.2);
- Concomitant therapy given (or other action taken);
- Action taken with respect to the IMP.

If an AE increases in severity it will be recorded as a new record with the same AE identifier.

AE data should be obtained through observation of the patient, from any information volunteered by the patient and through patient questioning. The patient may be asked "Do you have any health problems?" or "Have you had any health problems since your last site visit?"

Reporting of Signs and Symptoms versus a Diagnosis
Recording a diagnosis (when possible) is preferred to recording a list of associated signs and symptoms. However, if a diagnosis is known but there are associated signs or symptoms not generally attributed to the diagnosis, the diagnosis and each sign or symptom must be recorded separately.

Pregnancy
Should a pregnancy occur in a female patient or the partner of a male patient, it must be reported promptly, within 24 hours of the site first becoming aware of the pregnancy, by entering the pregnancy as a non-serious AE in the CRF and completing, signing, and dating the pregnancy report form. The pregnancy report form should be sent to the safety vendor using the contact details in Section 9.2.3. A pregnant patient should discontinue treatment, but remain in the study for ongoing assessments until the birth of the baby.

9.2.1 Definition of Severity of Adverse Events

Severity of any AE will be graded using the definitions below.

Definition of Severity of Adverse Events	
Mild	Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing])
Severe	Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable]).

Note: Severe is a measure of intensity whereas an event must meet one of the criteria for serious events listed in Section 9.1.2 to be considered **serious**; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 9.1.2. An AE that is assessed as severe should not be confused with a SAE.

9.2.2 Definition of Relationship of AEs to a Medicinal Product and/or Study Procedure

Site Investigator must assess the possible relationship between the AE and the IMP and record that assessment in the CRF.

The Sponsor will evaluate all SAEs with respect to expectedness according to the IB.

The relationship should be assessed according to the criteria below:

Probably Related	AEs that are temporally linked and for which the study product is more likely to be the explanation than other causes, which may improve when not using study product
Possibly Related	AEs that could equally well be explained by study product or other causes, which are usually temporally linked and may improve when not using study product but do not reappear when using study product
Not Related	AEs that can be clearly explained by extraneous causes and for which there is no plausible association with study product, or AEs for which there is no temporal relationship

9.2.3 SAE Reporting Procedure for Site Investigators

The Investigator must report (by fax or email) all SAEs to the safety vendor within 24 hours of awareness of an SAE by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and CRF, and sending the SAE form to the safety vendor by one of the following methods:

Study Contact for Reporting Serious Adverse Events

Please refer to the SAE Reporting Contact Details document.

If, for any reason, it is not possible to complete all sections of the SAE form within 24 hours, transmission of the form must not be delayed and the outstanding information should be sent on a follow-up SAE form.

Information on SAEs will be recorded on a SAE form. Blank copies are included in the study Investigator's file.

The SAE form must be completed as fully as possible with information relevant to the SAE(s) being reported. All fields should be populated or marked accordingly if no information is available.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, IRB/IEC, principal and coordinating investigators, trial investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country.

9.2.4 Follow-up SAE Reports

For all SAEs where important or relevant information is missing, active follow-up should be undertaken. The follow-up information must be presented on an SAE form marked as follow-up. It is necessary only to provide the new information, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IMP, and site number); this will allow the follow-up information to be linked to the initial SAE report, with the SAE form signed by an Investigator.

Specific information may be requested by the safety vendor using a follow-up request form.

Investigators or other site personnel should send relevant or requested anonymized supporting documentation (e.g. ECG, laboratory results, autopsy report) to the safety vendor.

The Investigator will ensure that all the necessary information is provided within the timelines stipulated by the safety vendor when the request for information is made.

Follow-up reports (as many as required) should be completed and submitted following the same procedure above.

9.3 Reporting Serious Adverse Events to the IEC/IRB

The Investigator is responsible for informing local IECs/IRBs of the applicable safety reports in compliance with local regulations. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigator's files and provided to Premier Research.

9.4 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

A suspected unexpected serious adverse reaction (SUSAR) is an SAE, the nature or severity of which is not consistent with the reference safety information of the study drug in the IB and for which there is at least a reasonable possibility of a causal relationship with the study drug.

The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the concerned authorities, central IECs/IRBs and Investigators, and in any case no later than seven days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs shall be reported to the concerned authorities, central IECs/IRBs and Investigators as soon as possible but within a maximum of fifteen days of first knowledge by the Sponsor. The Sponsor will report all SUSARs via FDA, the EudraVigilance Clinical Trials (CT) Module or Council for International Organizations of Medical Sciences (CIOMS) forms.

The Investigator is responsible for informing local IECs/IRBs of the applicable safety reports in compliance with local regulations. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigator's files and provided to Premier Research.

9.5 Adverse Event Reporting Period

AEs will be collected from the time of written informed consent until the end of the trial or patient withdrawal. All ongoing AEs will be followed until the follow-up telephone visit and SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up, whichever occurs first.

Any increase in transaminases > 3x ULN will be followed up (see section 9.6.2) until the the values have stabelised or the baseline level of the patient has been reestablished.

Any SAE (including an AE that leads to death) that occurs after the end of the trial, which the Investigator assesses as related to a trial procedure and/or medicinal product, should also be reported.

All new AEs or the worsening of any ongoing events from the time of informed consent will be recorded on the AE pages of the CRF.

9.6 Follow-up for specific laboratory abnormalities

9.6.1 Increased serum creatinine

Serum creatinine values > 2-3 fold compared to the patient's baseline value should be further investigated for signs of kidney injury. Estimation of the patient's GFR based on BUN, creatinine, and cystatin C should be performed. In addition, follow-up should be done according to local hospital guideline. Follow-up may include measurement of oliguria, urine analysis, glomerular filtration rate, vital signs, ultrasound of the kidney, blood sampling for parathyroid hormone, metabolic status, and investigation of other markers of kidney dysfunction and alternative causes of increased creatinine.

9.6.2 Increased transaminases

Transaminases (AST, ALT) > 3 x ULN must be further investigated in line with the FDA Guidance on Drug-Induced Liver Injury (64).

IBM patients may exhibit elevation in transaminases, and according to exclusion criteria 11, subjects are only excluded with clinically significant hepatic disease indicated by clinical laboratory assessment (results ≥3 times the upper limit of normal [ULN] for alanine aminotransferase combined with bilirubin ≥2 times the ULN. A consequence of this criteria is that subjects with ALT elevation not in the presence of bilirubin elevation may be eligible for the trial.

The investigator may apply clinical judgement to the threshold of transaminases that qualify for close monitoring. This will be based on the subject's baseline clinical safety laboratory results and the expected variability of such parameters under repeat measure. Exceptions to the guidance for close monitoring must be discussed with the medical monitor and the rationale behind any clinical judgement overruling the below definitions must be documented in the subjects medical/source records. Note that investigator judgment may not be applied to the guidance regarding IMP interruption or discontinuation (see Section 6.5.2).

Upon first observation of transaminases (AST, ALT) > 3 x ULN, a repeat test must be performed within 48-72 hours (ALT, AST, ALP, bilirubin) and the subject should be enquired for presence of symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash).

If the increase is confirmed, close observation must be performed:

- Repeating of ALT, AST, ALP, GGT, bilirubin, eosinophils (differential count) 2-3 times weekly. Frequency of retesting may be decreased to once a week or less (after agreement with the medical monitor) if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. The values should be monitored until the values have stabelised or the baseline level of the patient has been re-established.
- Obtaining/confirming detailed history of symptoms and prior or concurrent diseases.
- Obtaining/confirming concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease (e.g. performing an abdominal ultrasound or Magnetic resonance cholangiopancreatography (MRCP)).
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

If close observation is not possible, IMP must be interrupted or discontinued (see section 6.5.2.2)

If the subject cannot attend the trial site for close monitoring, the analyses may be conducted at a local laboratory.

At the earliest possible opportunity, a single serum sample should be taken for use in case further analyses to explore possible mechanisms behind the transaminase elevations are conducted.

The sample may be processed and shipped under ambient or frozen conditions and will be stored frozen at the central laboratory. This sample will be discarded as soon as it is decided that such analyses are not warranted or after sample processing and analysis is completed which will be no longer than 2 years after the completion of the trial.

All local laboratory assessments and other assessment performed in relation to increased transaminases must be recorded in the CRF including the appropriate reference ranges.

For scenarios where a permanent halt in the IMP is required, see Section 6.5.2.2

9.7 Study Halting Rules

All attempts will be made to enhance patient compliance (see Section 7.9). Early withdrawal may occur for any of the reasons listed in Section 6.5.1.

If the patient needs to discontinue study medication, every effort will be made to encourage the patient to continue with the study visits until study completion. If a patient is unable to return to the center, a phone call will be made to the patient. In the event of a loss to follow-up, information about the patient will be sought from the family or family physician.

9.8 Study Discontinuation

Please see Section 6.5.2.

9.9 Safety Oversight

The Premier Research medical monitor will be responsible for independent review of the safety laboratory tests and adverse events, will be responsible for monitoring the real-time reporting of SAEs, and will review laboratory reports and adverse events monthly, or more frequently as needed. The medical monitor will be blinded to treatment assignment. If the medical monitor has concerns regarding the safety data, they may notify the DMC. The medical monitor may request additional or clarifying information from the coordinating center of the treating physician. The medical monitor will prepare a report to present to the DMC prior to their meetings.

9.10 Data Monitoring Committee

A DMC will assess safety and tolerability at regular intervals. The responsibilities of the DMC are further described in a DMC charter.

10 CLINICAL MONITORING

Premier Research is responsible for ensuring the proper conduct of the clinical trial with regard to protocol adherence and validity of the data recorded in the CRFs. Premier Research will conduct site visits to monitor the trial and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) will visit the investigator and trial site at periodic intervals and maintain periodic communication.

The site Investigator will be informed of anticipated in-person monitoring visits. He/she will also receive a notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or his/her Sub-investigator(s) and other appropriate staff will be available on the day of the visit to discuss study conduct.

For additional information, please refer to the clinical monitoring plan.

11 STATISTICAL CONSIDERATIONS

11.1 General Considerations

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, a two-sided significance level of 5% will be used for all hypothesis testing.

Every effort will be made to retain subjects in this trial, to promote adherence to the study protocol, and to collect all data at every visit. If a subject cannot tolerate (even after tapering down) or refuses to continue taking study medication, we will continue to follow and evaluate that subject. If a subject withdraws from the trial, attempts will be made to bring the subject in for a final evaluation. Compliance with trial procedures, subject disposition, and reasons for subject withdrawal will be carefully tracked throughout the study.

11.2 Statistical Hypotheses

The primary outcome variable is the change from baseline to Month 20 in the total score on the IBMFRS. The null hypothesis to be tested is that the mean value of this outcome variable is the same in the arimoclomol and placebo groups. The alternative hypothesis is that the mean value differs between the groups (two-sided).

11.3 Analysis Populations

The following analysis populations are planned for this trial:

- **Intent-To-Treat Population (ITT) or Full analysis set (FAS):** The ITT/FAS population includes all randomized patients. Patients in the ITT population will contribute to the evaluation ‘as randomized’.
- **Safety Population (SAF):** The SAF population includes all patients who receive any amount of trial medication. Patients in the SAF population will be analysed according to treatment actually received. The definition of “*actually received*” will be based on simple couting the number of days on either of the two treatments. Further details will be provided in the SAP.

11.4 Description of Statistical Methods

11.4.1 Baseline Descriptive Statistics

The distributions of demographic and clinical characteristics will be described for the treatment groups as well as the overall cohort using standard summary statistics.

11.4.2 Analysis of the Primary Efficacy Endpoint(s)

Analysis of the Primary Estimand

The analyses will be based on the FAS using all observations from schedueld visits (see SAP for details) regardless of treatment adherence and used of concomittant medication. The analysis is a Mixed Model for Repeated Measurements (MMRM). The independent effects included in the model are treatment interacting with visit, trial centre as a separate main effect and baseline IBMFRS interacting with visit. An unstructured covariance matrix for IBMFRS measurements within the same patient will be used, hereby assuming that measurements from different subjects are conditionally independent.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. The model assumed that data are missing at random (MAR). Under this assumption, the statistical behaviour of the missing data can be described by the observed data included in the model, thus, observed IBMFRS responses at all visits and the observed effects adjusted for in the model. Consequently, MAR will reflect adherence to protocol (not nessesarily adherence to treatment). Of note, an analysis based on MAR may attribute benefits to patients who withdraw from trial altogether regardless of the reason for discontinuation. By assuming MAR but allowing patients to remain under observation while no longer exposed to trial IMP means that the primary statistical analysis evaluates effectiveness of arimoclomol, thus targeting the primary estimand.

The null hypothesis to be tested is that the mean difference in the primary endpoint between arimoclomol and placebo is zero. The alternative hypothesis is that it differs from zero. If the null-hypothesis is rejected (two-sided p-value < 0.05), and if the estimated mean difference in the primary endpoint between arimoclomol and placebo is greater than zero, then the primary objective of the trial will be confirmed.

The analysis of the primary estimand and other methods for handling missing data (including imputation models) are further specified in the SAP.

Analysis of the Secondary Estimand

The change from baseline in IBMFRS total score will be assessed for the secondary estimand using an MMRM analysis like the one detailed above. The difference lie in the data used for analysis: This MMRM will be based on all observed IBMFRS-data from scheduled visits while patients were exposed to trial mediction (i.e. before treatment discontinuation (see SAP for further details)).

Explorative analysis

To explore the IBMFRS in further details, indiviual items and domains will be presented based on both in-clinic and telephone assessments. The planned analysis is further specificed in the SAP.

11.4.3 Analysis of the Secondary Endpoint(s)

The secondary outcome variables of efficacy including; 6MWT distance walked (at minutes 2 and 6) strength outcomes (quantitative quadriceps strength and MMT scores, grip strength), HAQ-DI, SF-36 scores, falls and near falls, CGIS, CGIC, PGIS, PGIC, and modified timed up and go (mTUG) will be analysed at month 12 and 20 for both the primary and secondary estimands. Further details on the analysis methods wil be provided in the SAP.

11.5 Safety Analyses

Adverse events will be summarized by treatment group, maximum severity, and perceived relationship to study medication.

Continuous measures of safety (vital signs, laboratory test results) will be presented using descriptive statistics and the C-SSRS will be summarized.

See the SAP for the full specification of the safety and tolerability analysis.

11.6 Adherence and Retention Analyses

Compliance data (pill counts) will be summarized by treatment group, overall and by visit. Subject disposition (study completion, study completion on a reduced dosage or off of study drug, withdrawal) will also be summarized by treatment group.

11.7 Planned Analyses

11.7.1 Safety Review

The sponsor will monitor blinded safety data on an ongoing basis and the DMC will monitor safety and tolerability according the DMC charter.

11.7.2 Additional Sub-Group Analyses

We will investigate the interactions between treatment group and selected baseline variables including site, IBMFRS score, 6-minute walk test distance, site of onset, and [redacted] status. This will be done by adding the appropriate main effect and interaction terms to the primary analysis model. Since the power to detect potentially meaningful interactions will be limited, the magnitudes of treatment effects in the relevant subgroups will be examined. The observation of clinically important subgroup differences in treatment effects (e.g., in those with low vs. high IBMFRS scores at baseline) will serve as hypothesis generation for possible future studies designed to specifically address the issue of differential therapeutic response.

11.7.3 Sensitivity Analyses

To investigate the sensitivity of the primary and secondary analysis results, complementary and separate analyses will be performed for each of the two estimands. In particular. these sensitivity analyses will be used to evaluate the sensitivity of the results due to the impact of missing data. Further details are provided in the SAP.

11.8 Sample Size Considerations

The primary outcome variable is the change from baseline to Month 20 in the IBMFRS. In the arimoclomol pilot study, the standard deviation of the 12-month change in IBMFRS was 2.9. The mean change in the placebo group was -3.5 and the mean change in the arimoclomol group was -2.1. A sample size of 68 subjects per group (136 total) will provide 80% power to detect a treatment group difference in mean response of 1.4 points, using a two-sample t-test and a 5% significance level (two-tailed). To account for an anticipated 10% drop-out rate, the sample size will be inflated to 75 participants per group (150 total). Although this calculation strictly applies only to a trial with 12-month follow-up, it will also apply to this trial if, as expected, the magnitude of the treatment effect relative to the magnitude of the standard deviation of the change in IBMFRS score does not diminish over time.

11.9 Measures to Minimize Bias

11.9.1 Breaking the Study Blind/Participant Code

Each site will receive documentation to break the randomization code if needed. The site investigators will not have access to the randomization codes. The investigator or pharmacist at the site will have access to the unblinded information for the double-blind treatment for each subject via code envelopes.

The investigator may only break the code for a subject if knowledge of the IMP is necessary to provide optimal treatment to the subject in an emergency situation. If possible, the investigator should consult the Medical Monitor before breaking the code. The investigator must record the date, time, and reason for breaking the code on the code envelope and sign it. The subject must be immediately withdrawn from IMP and followed up according to Section 6.5.

11.9.2 Unblinding for Data Monitoring Committee

Periodic safety review by the Data Monitoring Committee will be facilitated by an unblinded statistician from Premier not otherwise involved in the study. The sponsor and all other study personnel will remain blinded. Safety reports will be reviewed by the DMC in a closed session. If the recommendation by the DMC is to continue the study, the detailed results of the safety review will not be conveyed to the sponsor until the end of the study. In the event that the DMC recommends stopping the study, communications between the DMC and the sponsor will be strictly limited to a small number of designated sponsor representatives. The sponsor will share DMC recommendations with the Steering Committee promptly. The details of the DMC process, including communications with the sponsor, will be detailed in the DMC charter and the statistical analysis plan.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF is required and should be completed for each included (consented) patient. The Investigator will be responsible for the accuracy of the data entered into the CRF. All data must be entered in English and must be completed by designated study personnel. The completed CRFs must be reviewed, and electronically signed/dated by the Investigator in a timely fashion. If a change is made on any of the eForms after the Investigator has signed that eForm, the Investigator must re-sign the CRF. Relevant completed eForms must be available for review at each scheduled monitoring visit.

The Investigator will allow designated sponsor representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the CRFs.

Source documents (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial. Source documents should be available to support all the data recorded in the CRF. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient included in this clinical trial.

13 QUALITY ASSURANCE AND QUALITY CONTROL

An independent audit of the study may be conducted during the study or after completion. The audit may be conducted by either Orphazyme or an independent auditor or a regulatory authority.

13.1 Quality Control

Quality Control (QC) is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled. QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 Quality Assurance

Quality Assurance (QA) is defined as the planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

13.3 Audit

The Investigator will permit an audit mandated by the Sponsor after reasonable notice. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP and applicable regulatory requirements, that the rights and well-being of patients enrolled have been protected and that all data relevant for the evaluation of the IMP have been captured, processed and reported in compliance with the planned arrangements. The Investigator will permit direct access to all study documents, IMP accountability records, medical records and source data. The Investigator and his/her study team will also be available for discussion regarding study progress and procedures during the audit (both during the audit and at the end of the audit for an “exit” discussion).

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Institutional Review Board

It is the responsibility of the local site Investigator to obtain approval of the trial protocol/amendments from the IEC/IRB. Prior to the initiation of the study, each site Investigator will submit the following documents to the appropriate IECs/IRBs for approval:

- The study protocol and any amendments;
- The IB;
- Details of any compensation to patients*;*
- The current *curriculum vitae* of the Principal Investigator;
- Any other requested document(s).

A copy of the approval will be sent to Premier Research along with all other correspondence with the IEC/IRB, including the submission documents. The Investigator should file all correspondence with the IEC/IRB in the Investigator site file.

The study will not start and no subject may undergo any procedure not part of routine care for the subject's condition until approval of the protocol and the consent form has been obtained from the appropriate IEC/IRB. The letter of approval should be dated, and should specify the protocol number and date of the protocol or amendment which was reviewed and approved. It should also specify the date the ICF was reviewed and approved.

A dated list of the voting members of the IEC/IRB who were present when the protocol was reviewed and approved, including their titles/occupations and institutional affiliations should be provided where possible by the Investigator to Premier Research prior to study initiation. The Investigator will make all attempts to ensure that the IEC/IRB is constituted and operates in accordance with the ICH-GCP and any local regulations.

The Investigator will submit any protocol amendments to the IEC/IRB (and other local authorities, according to local regulations) prior to implementation.

The Investigator will submit required progress reports to the IEC/IRB that approved the protocol at least annually, as well as report any SAEs, life-threatening problems or deaths, to comply with ICH-GCP. The Investigator must inform the IEC/IRB of the termination of the study.

14.2 Regulatory Body Approval

The study will not be started until the sponsor has received approval from relevant regulatory bodies. The sponsor will provide the Investigator with a copy of the relevant document.

14.3 Informed Consent and Screening Data

Any changes requested by the IEC/IRB must be approved by the IEC/IRB prior to the documents being used. A copy of the final, IEC/IRB-approved consent form must be submitted to Premier Research prior to initiation of this study.

Written informed consent will be obtained from each patient prior to inclusion in the trial, and prior to any study-related assessments are performed.

14.3.1 Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or companies supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data for purposes of statistical analysis and scientific reporting will be transmitted to and stored at Premier Research and the University of Rochester. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research and University of Rochester staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

The Investigator must ensure that the patients' anonymity will be maintained.

The Investigator should keep a separate log (Patient Master List) of patient's codes (assigned patient number), names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the sponsor (e.g. signed informed consent forms) should be maintained by the Investigator in strict confidence.

14.3.2 Staff Information and Responsibilities

It is the responsibility of the local site Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed to allow collection of accurate, consistent, complete and reliable data.

The local site Investigator will provide a list of delegated responsibility to Premier Research, detailing the various study tasks to be performed by each member of his/her study staff. Each staff member should sign in agreement to their performing each of the tasks delegated to them on the list. The local site Investigator should ensure that the staff have the required knowledge and training for the tasks delegated to them.

14.3.3 Essential Document Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while ensuring confidentiality of the trial patients' personal data. Documents that enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and show whether the trial is, or has been, conducted in accordance with ICH-GCP and applicable regulatory requirements are considered essential documents.

The Investigator will retain copies of all the essential documents (as defined by ICH-GCP) until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. The period of document retention is, however, also dependent on the applicable regulatory requirements (e.g. EEC Directive 91/507 requires retention of patient codes for at least 15 years after the completion or discontinuation of a trial and retention of hospital records and other source data for the maximum time permitted by the institution where the study takes place). The Investigator should take measures to prevent accidental or premature destruction of these documents.

The essential documents include: the signed protocol, copies of the completed CRFs, hospital records and other source documents, IEC/IRB approval and all related correspondence, including approved documents, and all other documentation included in the Investigator site file.

The Investigator will inform the Sponsor of the storage location of these essential documents and must contact the Sponsor before disposing of any. If the Investigator wishes to assign the files to someone else (e.g. if he/she retires) or to remove them to another location, the Sponsor Project Manager should be consulted about this change.

The Sponsor will inform the Investigator in writing when these documents no longer need to be retained.

14.4 Data Handling and Record Keeping

14.4.1 Data Collection and Management Responsibilities

Data will be collected and entered into an electronic data capture system (Datalabs) provided by Premier Research Inc. Datalabs is a web-based 21 CRF Part 11-compliant database system which will be customized specifically for this clinical trial. Premier Research will be responsible for managing the database. Drug dispensing logs will be kept to record the total amount of medication received from and returned to the site. Completed informed consent forms from each subject will be available in the subject's file and verified for proper documentation.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the local site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and the timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents will be stored at each of the clinical sites in double locked storage.

Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Datalabs. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The site investigators will be responsible for insuring that all blank data spaces on each CRF are filled in. The Premier DM group will notify each investigator of any missing or inconsistent data. All completed CRFs are to be reviewed by the site investigator.

14.4.2 Protocol Adherence

The study PI will work closely with PIs at all other sites to ensure adherence of the protocol by the study sites and study data integrity. The Sponsor PI will be responsible for communicating with all sites to ensure smooth conduct of the study and prompt data submission. The PI will coordinate e-mail and conference call communications and work with the data coordinator to prepare monthly reports from each site indicating the status of the study and problems that might arise. Serious adverse events will be reported immediately to the Sponsor PI and reviewed promptly by the medical safety monitor.

Based upon our previous experience in managing multicenter studies of neuromuscular disorders at KUMC, we will again assemble a communications and computing infrastructure and technical staff to ensure the success of this study. We will use strategies for intra- and inter-site communication, data entry, storage, management, and analysis similar to those we have previously used and currently use. We will have several ways to ensure adequate communication between the data center and the individual clinical sites. Telephone, fax, and electronic mail will be the primary modes of inter- and intra-site communication for investigators and study staff. The existing infrastructure at each site includes sophisticated telephone networks, voice messaging systems, fax machines and Ethernet connections to the Internet to support this strategy. All study computers at the data center and each of the clinical sites will be password protected, and kept in locked offices. The evaluators performing the monthly studies will complete a CRF after each visit. The PI/study coordinator will be responsible for dispensing and accounting for all study medication. The PI at each study site is responsible for all aspects of the study at the site. The investigator agrees to cooperate fully with monitors.

14.4.3 Data Storage and Backup

Data backup, restore and security will be handled as per Premier Research's Data Management Plan

14.4.4 Study Records Retention

Study records must be retained for 5 years after the close of the study or until the drug is approved for two years by the FDA.

14.4.5 Protocol Deviations

The trial must be conducted in accordance with:

- The protocol;
- Applicable regulatory requirement(s) or conditions linked to the approval(s) of the study;
- Applicable IEC/IRB requirement or conditions linked to the approval(s) of the study;
- Any particulars or documents, other than the protocol, accompanying the regulatory or IEC/IRB request or that application.

Protocol waivers will not be granted. Any amendment(s) to the protocol must be approved by both Orphazyme A/S and the IEC/IRB which granted the original approval of the study prior to their implementation (unless only logistical or administrative aspects of the trial are involved). All substantial amendments to the protocol must be approved by the applicable regulatory bodies prior to their implementation.

However, in the event of any medical emergency, the Investigator is free to institute any medical procedure he/she deems appropriate. Such events and procedures must be promptly reported to the Orphazyme A/S representatives.

14.4.6 Publication and Data Sharing Policy

The study will be registered at www.clinicaltrials.gov. By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals.

As the study is a multi-centre study, any publication based on the results obtained at the Institution shall not be made before the first multi-centre publication describing the primary results has been published. If a publication concerns the analyses of sub-sets of data from the Trial, the publication shall make reference to the relevant multi-centre publication(s). Upon completion of the Trial, and any prior publication of multi-centre data, or when the Trial data are adequate (in Orphazyme's discrete and reasonable judgement), the Institution may prepare the data deriving from the Trial for publication. The publishing Investigator(s) will not make any publication or other public disclosure, whether oral or written, which includes any study data or which describes any work carried out using the study drug unless a draft of such proposed publication or other public disclosure has been provided to UCL ([redacted] and [redacted]) and to KUMC ([redacted] and [redacted]) and to other members of the Scientific Steering Committee who will also perform the review for the Muscle Study Group and to Orphazyme A/S for review at least forty five (45) days prior to any such submission for publication or public disclosure. During such forty five (45) day period, Orphazyme A/S may require that any publication or other public disclosure is delayed for up to four (4) months to permit adequate steps to be taken to secure patent or other protection of the subject matter referred therein and/or to require the deletion of any Confidential Information that would be disclosed by such publication or public disclosure. After Orphazyme has secured that intellectual property protection of the subject matter and/or Orphazyme has released the manuscript for publication, the publishing Investigator(s) may submit the proposed publication to outside reviewers or publications for review.

In any publication or public disclosure, whether oral or written, which mentions the study, the publishing Investigator(s) will acknowledge Orphazyme A/S.

Orphazyme A/S may use all such publications and public disclosures at its own discretion, including the use for regulatory submissions.

15 STUDY ADMINISTRATION

15.1 Study Leadership

A Scientific Steering Committee will govern the conduct of the study and provide scientific direction. The Steering Committee composition is given in protocol section 2. The Steering Committee will meet and act according to the Steering Committee Charter.

16 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the FDA-OPD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 CORONAVIRUS (COVID) OPERATIONAL CHANGES

The document (COVID-19) Addendum 1.0 dated 24-Mar-2020 shall remain in effect with this Clinical Trial Protocol. The Addendum to the Clinical Trial Protocol is designed to mitigate the operational impact resulting from COVID-19, and shall only be applied as an interim solution during the period that normal Clinical Trial Protocol logistics cannot be adhered to. Once containment measures have ceased and operations return to normal on both a site and subject level, procedures will resume as per the site's currently approved Clinical Trial Protocol.

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APPENDIX 1: EUROPEAN NEUROMUSCULAR CENTRE INCLUSION

European Neuromuscular Centre Inclusion Body Myositis research diagnostic criteria 2011			
Diagnostic sub-group	**Clinico-pathologically defined IBM**	**Clinically defined IBM**	**Probable IBM**
Clinical features			
Duration of weakness > 12 months	X	X	X
Age at onset > 45 years	X	X	X
Creatine kinase ≤ 15x ULN	X	X	X
FF weakness > SA weakness ***AND/OR*** KE weakness ≥ HF weakness	X	-	-
FF weakness > SA weakness ***AND*** KE weakness ≥ HF weakness	-	X	-
FF weakness > SA weakness ***OR*** KE weakness ≥ HF weakness	-	-	X
Pathological features			
Endomysial inflammatory infiltrate	X	≥1, but not all of the 4 pathological features	≥1, but not all of the 4 pathological features
Rimmed vacuoles	X		
Protein accumulation* or 15-18nm filaments	X		
Up-regulation of MHC Class I	-		
*Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). FF, Finger flexion; HF, Hip flexion; KE, Knee extension; SA, Shoulder abduction; MHC Class I, Major histocompatibility complex class I; ULN = Upper limit of normal.			

APPENDIX 2: IBM FUNCTIONAL RATING SCALE

1. SWALLOWING
- 4 Normal
- 3 Early eating problems – occasional choking
- 2 Dietary consistency changes
- 1 Frequent choking
- 0 Needs tube feeding

2. HANDWRITING (*with dominant hand prior to IBM onset)*
- 4 Normal
- 3 Slow or sloppy; all words are legible
- 2 Not all words are legible
- 1 Able to grip pen but unable to write
- 0 Unable to grip pen

3. CUTTING FOOD AND HANDLING UTENSILS
- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can cut most foods, although clumsy & slow; some help needed
- 1 Food must be cut by someone but can still feed slowly
- 0 Needs to be fed

4. FINE MOTOR TASKS ***(opening doors, using keys, picking up small objects)***
- 4 Independent
- 3 Slow or clumsy in completing task
- 2 Independent but requires modified techniques or assistive devices
- 1 Frequently requires assistance from caregiver
- 0 Unable

5. DRESSING
- 4 Normal
- 3 Independent but with increased effort or decreased efficiency
- 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.)
- 1 Requires assistance from caregiver for some clothing items
- 0 Total dependence

6. HYGIENE ***(Bathing and toileting)***
- 4 Normal
- 3 Independent but with increased effort or decreased activity
- 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.)
- 1 Requires occasional assistance from caregiver
- 0 Completely dependent

7. TURNING IN BED & ADJUSTING COVERS
- 4 Normal
- 3 Somewhat slow & clumsy but no help needed
- 2 Can turn alone or adjust sheets but with great difficulty
- 1 Can initiate but not turn or adjust sheets alone
- 0 Unable or requires total assistance

8. SIT TO STAND
- 4 Independent (without use of arms)
- 3 Performs with substitute motions (leaning forward, rocking) but without use of arms)
- 2 Requires use of arms
- 1 Requires assistance from device/person
- 0 Unable to stand

9. WALKING
- 4 Normal
- 3 Slow or mild unsteadiness
- 2 Intermittent use of assistive device (AFO, cane, walker)
- 1 Dependent on assistive device
- 0 Wheelchair dependent

10. CLIMBING STAIRS
- 4 normal
- 3 Slow with hesitation or increased effort; uses handrail intermittently
- 2 Dependent on handrail
- 1 Dependent on handrail and additional support (cane or person)
- 0 Cannot climb stairs

APPENDIX 3: [redacted] SUB-STUDY

This was an exploratory sub-study and the details are not relevant for the primary or secondary endpoints and therefore not included here.

Addendum 1.0 to

Clinical Trial Protocol v9.0 dated 08-Jun-2020

Phase 2/3 Study of Arimoclomol in Inclusion Body Myositis (IBM)
A Randomized, Double-blind, Placebo-Controlled Trial

Sponsor: Orphazyme A/S, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark
International Coordinating investigator: [redacted], MD, Professor of Neurology
Protocol number: IBM4809
EudraCT No.: 2017-004903-33
ClinicalTrials.gov Identifier: NCT02753530
Trial product name: Arimoclomol Capsules

Date of Addendum: 23-Sep-2020

The trial will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements

Contents

Justification for Addendum

Results from an in vitro study showed that arimoclomol is a direct inhibitor of CYP2D6 with an IC50 of190 µM which is > 25 times higher than clinical exposure (Cmax)

The investigator's Brochure was previously updated with these findings and correspondingly the Clinical trial Protocol (CTP) was updated to indicate that concomitant treatment with CYP2D6 substrates should be done with caution (since their exposure could increase as a result of their metabolism being inhibited).

By using mechanistic static modelling, instead of basic equations, it has since been evaluated that the in vitro CYP2D6 inhibition is not clinically relevant. These findings have been included in the annual update of the Investigator's Brochure and the updated guidance on use of concomitant medications are included in this CTP addendum.

The changes described are done to ensure continued safety and well-being of the subjects and the integrity of the clinical trial. A sponsor risk assessment has concluded that the changes in this addendum are not likely to affect the safety and well-being of the participants or the scientific value of the trial. Therefore, the Sponsor confirms that the benefit-risk evaluation for arimoclomol in IBM is not changed.

Modification to the Clinical Trial Protocol due to the release of Investigator Brochure version 4.0 dated 15-SEP-2020

The following changes shall be made to the respective sections of the Clinical Trial Protocol version 9.0.

The below table provides a detailed description of changes made to protocol content as part of this protocol addendum.

Text in *italics* represents additions

Text in ~~strikethrough~~ represents deletions

Section	***Modification***	***Rationale (including risk/benefit justification)***
8.4 Precautionary Medications, Treatments, and Procedures	Arimoclomol is an in vitro inhibitor of the OCT2, MATE-1, and MATE-2K transporters and consequently may inhibit the elimination of cationic drugs that are significantly eliminated by tubular secretion. In addition, arimoclomol is an in vitro substrate of the MATE-1 and MATE-2K transporters. Arimoclomol undergoes renal tubular secretion, and concomitant treatment with drugs that are MATE-1 or MATE-2K inhibitors may therefore lead to increased exposure of arimoclomol. Consequently, the concomitant use of cationic drugs that are significantly eliminated by tubular secretion as well as drugs that are MATE-1 or MATE-2K inhibitors should be administered with caution. These include, but are not limited to, amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide,	There is no change the benefit-risk evaluation as a result of this change. Information is provided to the investigators to ensure guidance in line with the Investigators Brochure update.

Section	*Modification*	*Rationale (including risk/benefit justification)*
	ranitidine, varenicline, oxaliplatin, dofetelide, trimethoprim, quinidine, verapamil, levofloxacin, ciprofloxacin, moxifloxacin, pyrimethamine, and ondansetron. ~~Additionally, in vitro studies show that arimoclomol is a direct inhibitor of CYP2D6 and may potentially cause increase in exposure of co-administered medications that are substrates of CYP2D6 when arimoclomol is dosed at 400 mg t.i.d. Since, the magnitude of the potential increase cannot be predicted from in vitro data caution is advised if arimoclomol is co-administered with medicinal products that are metabolised by CYP2D6. This may for examples be relevant for class I anti arrhytmics, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI's) particularly if they are known to be sensitive and moderate sensitive CYP2D6 substrates and/or have a narrow therapeutic index. The product information for co-administered medicinal products should be consulted for guidance on concomitant treatment with a CYP2D6 inhibitor as dose adjustment of the CYP2D6 substrate may be appropriate. For compounds metabolised by CYP2D6 the dose may be reduced and for pro-drugs that are converted to the active compound by CYP2D6 the dose may be increased to ensure efficacy.~~ *Based on in vitro studies, drug interactions related to cytochrome P450 (CYP) enzymes are not expected. Even though CYP2D6 inhibition was observed in vitro, the mechanistic static model predicts that it will not be clinically relevant. Consequently, concomitant use of drugs that are CYP2D6 substrate is not considered to of concern.*	

Section	*Modification*	*Rationale (including risk/benefit justification)*
	Animal studies have indicated a possible interaction with furosemide (additive effect) and enalapril (decreased effect), both at high doses, and consequently concomitant dosing should be done with caution.	